Editorial

Causes of Death in Japan with Special Reference to the Death of Cardiovascular Origin

WITH the world trend of increasing number of the cardiovascular disease, the mortality rates of major causes of death in Japan have also shown significant changes during the past thirty years (Fig. 1). Tuberculosis

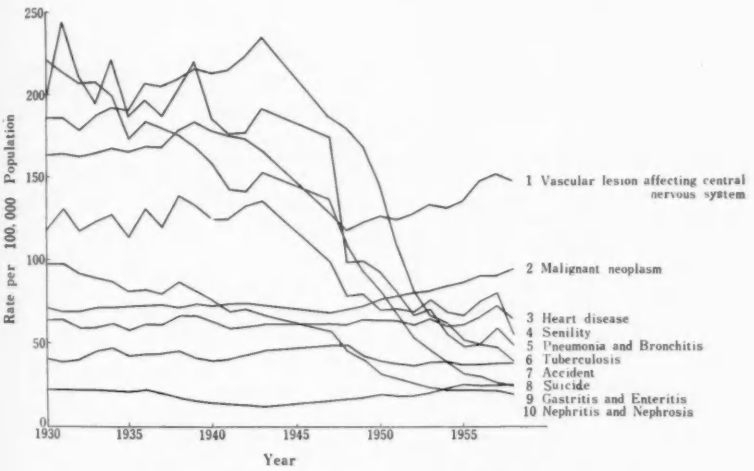

Fig. 1. Mortality for major causes of death in Japan (1930–1958).

which had been the leading cause of death until 1950 fell to the sixth place in 1957. Pulmonary diseases, such as pneumonia and bronchitis, and alimentary tract diseases, such as gastritis and enteritis, which were the most important causes of death in early period of 20th century, decreased sharply after World War II, and they now occupy the fifth and ninth place respectively. On the other hand, the deaths from the vascular lesion affecting central nervous system attained the first and those from heart disease the third place with a tendency of progressive increase in each year.

Most of the vascular lesions affecting central nervous system are cerebral hemorrhage and encephalomalacia mainly due to hypertension. The total number of deaths by cerebral vascular accidents averaged 100,000 per year until 1951 ; then increased to 130,000 in 1956. The rate to the total deaths was only 10% in 1935, and has increased to 20% in 1958 (Fig. 2). Likewise, the rank, which was the fourth in 1935, gradually became higher

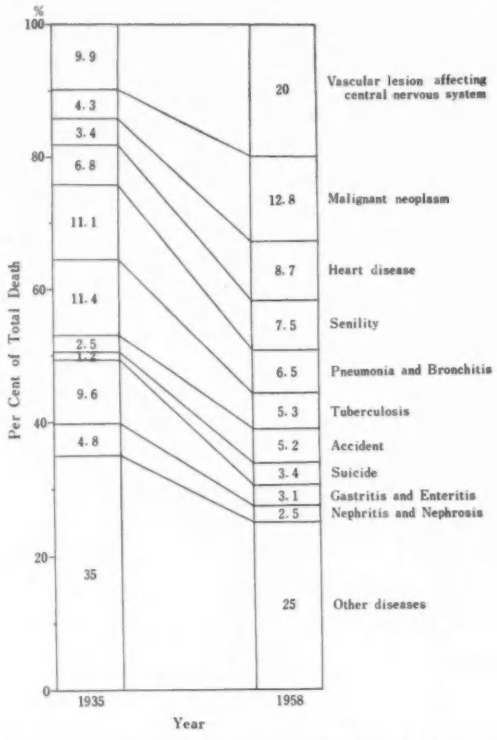

Fig. 2. Rates of selected causes of death to the total deaths.

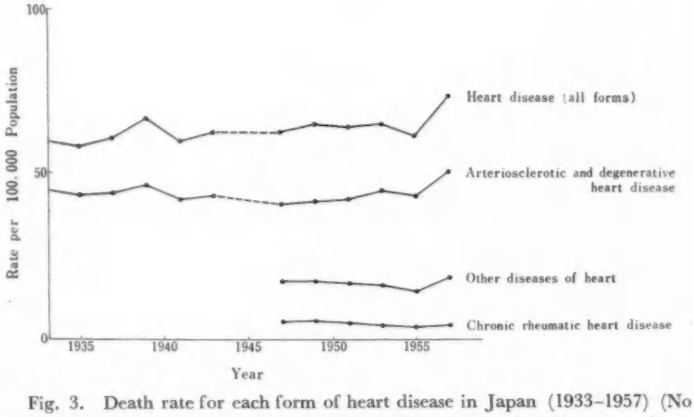

Fig. 3. Death rate for each form of heart disease in Japan (1933–1957) (No data are available for chronic rheumatic heart disease and other diseases of heart before 1947).

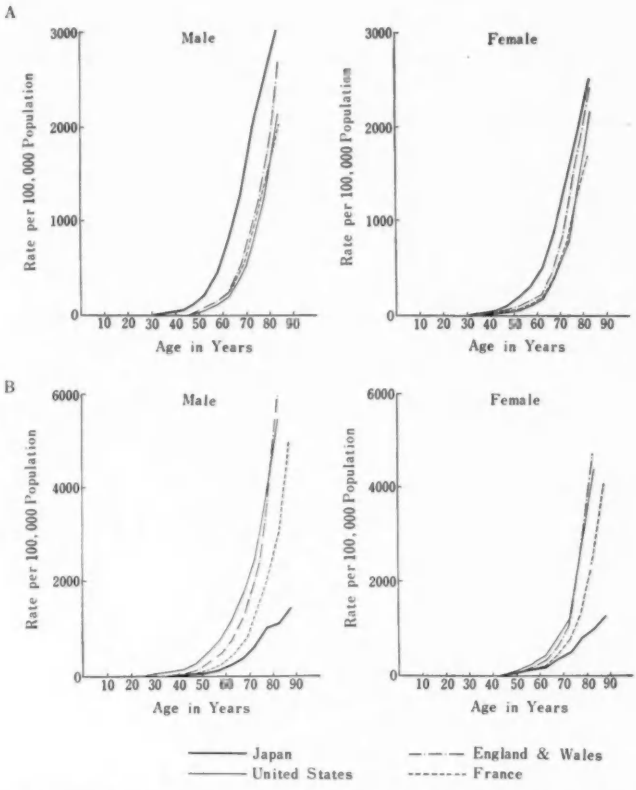

Fig. 4. Mortality from cardiovascular causes in 1955 according to sex and age in selected countries.*

A: Vascular lesions affecting central nervous system

B: All forms of heart disease

* Taken from Annual Epidemiological and Vital Statistics, W.H.O., 1955.

until it finally reached the top in 1951 and has remained thereafter.

The total number of deaths by heart disease was about 40,000 in 1948 and has increased at a rapid rate to a point where it exceeded 60,000 in 1957. The rate to the total deaths was only 3.4% in 1935 but became 8.7% in 1958 (Fig. 2).

Evaluation in this increasing death rate by the heart disease requires a detailed analysis. The different groups of heart disease best can be classified as arteriosclerotic and degenerative heart disease, chronic rheumatic heart disease and other diseases of the heart according to the international statistical classification. When the recent changes in death rate in the these three groups are shown (Fig. 3), it is apparent that an increase in the mortality rate from all forms of heart disease is attributed to the increased death from arteriosclerotic and degenerative heart disease.

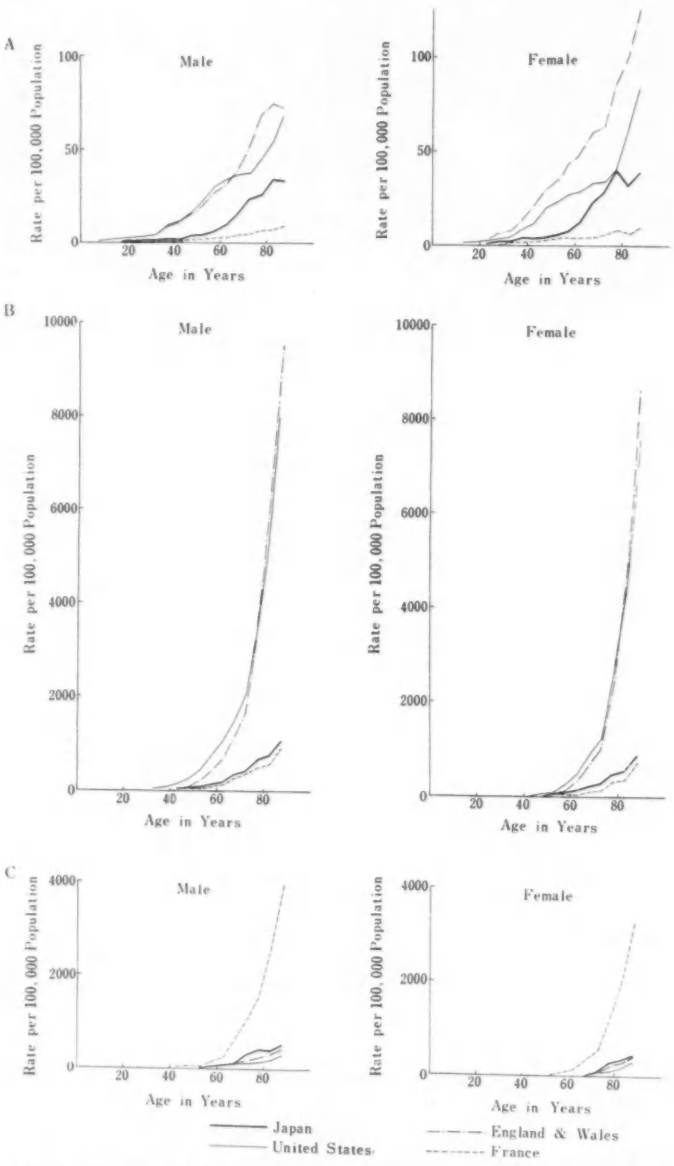

Fig. 5. Mortality from three groups of heart disease in 1955 according to sex and age in selected countries.*

A: Chronic rheumatic heart disease

B: Arteriosclerotic and degenerative heart disease

C: Other diseases of heart

* Taken from Annual Epidemiological and Vital Statistics, W.H.O., 1955.

Comparing the results obtained with those in foreign countries, the higher rate of vascular lesion affecting central nervous system and the lower incidence of heart disease in Japan is apparent (Fig. 4). When the deaths from three groups of heart disease are plotted against the age and sex (Fig. 5), the incidence of rheumatic heart disease is in the position between that in United States and England and that in France. The rate of arteriosclerotic and degenerative heart disease is far less than that in United States and England, and nearly equals to that in France. These interesting facts have drawn particular attention of many investigators in the field of cardiovascular disease.

For the reasons of these facts, differences in epidemiological, nutritional and environmental factors have been suggested, though they should remain to be investigated further. We hope that the recent advancements in cardiovascular research in many countries will someday resolve this problem which will undoubtedly be a great contribution to the welfare of the human race.

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Cerebral Embolism in Cardiac Diseases—The Clinical and Pathological Studies of 56 Cases

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Clinical and pathological studies on 56 cases of cerebral embolism were made among 1,029 admitted cardiac patients. The incidence of cerebral embolism was greatest in mitral valvular disease. The age of patients and the intervals between the episodes were studied. The relationship of the occurrence of cerebral embolism to the atrial fibrillation, the heart size, administration of digitalis and congestive failure was also examined. The laterality of hemiplegia was not obvious. Recoveries from the mental disturbance was complete in 79% of 42 cases. In autopsied cases, a correlation between cerebral embolism and mural thrombosis was found, and the locations of lesions in the brain and involved arteries were also studied.

IN recent years, cerebral vascular accidents have become the most important cause of death in Japan as well as in other countries. According to statistical analysis, 90% of the fatal cases with cerebral vascular accident is due to the cerebral hemorrhage, and only 5 to 6% of them is due to the cerebral embolism or thrombosis. It is generally accepted, however, that the deaths of cerebral malacia have been gradually increasing in number. According to Popper,[1] 13.8% is due to the cerebral embolism among 564 deaths of cerebral vascular accidents. Unfortunately, there have been only few clinical and pathological studies for cerebral embolism published in Japan in the past.

The improvement of diagnostic technique of cerebral angiography and recent advance in cerebral and cardiac surgery together with anticoagulant therapy make it worthwhile to re-evaluate the cerebral embolism.

In the present study, the cerebral embolic cases were collected from the group of cardiac patients admitted to the Second Medical Department, Tokyo University Hospital and the autopsy findings were correlated with clinical pictures.

Materials and Results

One thousand and twenty-nine patients suffered from various heart

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Table I. Incidence of Cerebral Embolism among 1,027 Cases* with Cardiac Disease

	Male		Female		Total	
	Total number	No. of embolic cases	Total number	No. of embolic cases	Total number	No. of embolic cases
M.I.	5	0	25	0	30	0
M. S. I., M. S.	61	8	130	16	191	24
C. V. D.	55	8	54	3	109	11
A.	69	2	25	0	94	2
H. C. V. D. A. H. D.	211	4	92	3	303	7
Cong. H. D.	43	2	47	0	90	2
S. B. E.	38	6	31	4	69	10
Miscellaneous	84	0	59	0	143	0
Total	566	30 (5.3%)	463	26 (5.6%)	1029	56 (5.4%)

Note: M.I.: Mitral insufficiency
M.S.: Mitral stenosis
M.S.I.: Mitral stenoinsufficiency
C.V.D.: Combined valvular disease
A.: Aortic valvular disease
H.C.V.D.: Hypertensive cardiovascular disease
A.H.D.: Atherosclerotic heart disease
Cong. H.D.: Congenital heart disease
S.B.E.: Subacute bacterial endocarditis

* Cases admitted to the Second Medical Department, Tokyo University Hospital between 1941 and 1959.

diseases were admitted to the Second Medical Department from 1941 to 1959. An extensive study in their case histories indicated that 56 cases had one or more clinical cerebral embolic episodes before or during the admission to the hospital. Of these, 30 cases were male and 26 were female.

The incidence of cerebral embolism among the admitted cardiac patients was 5.3% for male and 5.6% for female (Table I). The results which are essential for the discussion will be mentioned at each category.

Discussion

Cause of Cerebral Embolism—

It is well known that the important causes for cerebral embolism are mitral stenosis or other valvular diseases, myocardial infarction, stubacute bacterial endocarditis (S.B.E.), atherosclerosis of the ascending aorta and others.

The nature of the original cardiac disease in our 56 patients with cerebral embolism is shown in Table I. Twenty-four cases had mitral valvular disease at the time of embolic episode, 11 had combined valvular disease, and 10 had S.B.E. Among 424 admitted patients with valvular disease, 36 (8.7%) had cerebral embolic episode, and in 69 cases with S.B.E., there were 10 cases (14.5%) of cerebral embolism. These incidences of cerebral embolism were much greater than that of patients with hypertensive and sclerotic heart disease (2.3%) or congenital heart disease (2.2%). In valvular heart diseases, the incidence of cerebral embolism was 12.6% in cases with mitral stenosis (MS) and with both stenosis and insufficiency (M.S.I.), and 10.1% in combined valvular disease (C.V.D.). These values were greater than that of aortic valvular disease (2.1%) or mitral insufficiency (0%) alone.

According to Wood[2], arterial embolisms occurred in 9 to 14% of the patients with mitral stenosis, 30% of whom had cerebral embolism. Keen and Leveaux[3] found 34 cases (20%)of cerebral embolism in 172 patients of rheumatic heart disease, and Weiss[4] stated that 23 of 48 autopsied cases with cerebral embolism had rheumatic heart disease. From our observation, as well as other studies, it is clear that the occurrence of cerebral embolism is not rare in the patients with valvular disease of the heart, especially that with mitral stenosis.

The cerebral embolisms due to S.B.E. were found in 13 (25.5%) of 51 cases with S.B.E. by Mikata,[5] and 16 (16.6%) of 72 cases by Clawson.[6] Morgan[7] stated that there were 69 deaths caused by cerebral embolism among 363 deaths by S.B.E. Thus, S.B.E. is another important cause of cerebral embolism.

In regard to the myocardial infarction, Jordan and his co-workers[8] found intracardiac mural thrombosis in 108 cases (51%) of 218 patients with myocardial infarction. This finding is in accordance with others[9]-[11] and they suggested that the mural thrombosis had potentiality to cause the cerebral embolism. In fact, Miller and his associates[12] observed 19 cases of cerebral arterial " occulsion " in 210 cases of acute myocardial infarction, and Doscher[13] found that the embolism occurred in 64 cases (2.7%) among 2,341 cases of myocardial infarction. On the other hand, in our series of 56 cases of cerebral embolism, there were only 2 cases of non-acute myocardial infarction. The reason for the fewer cases of cerebral emblism associated with myocardial infarction in our cases than that of other workers' is not known. It may be due to the epidemiological difference of races.

In recent years, there have been reported cases of the cerebral embolism caused by myxoma of the left atrium.[14][15] However, this is such a rare disease as only 8 cases were found in autopsied cases of 480,000.[16] And in our series, we found no case of myxoma.

Age at the time of the first embolic episode— (Table II)

The age at the time of the first embolic episode ranged from 14 to 77 years with a mean of 44 in all our cases and it was between 14 and 51 years

Table II. Age at First Embolic Episode in Patients with Mitral Stenosis, Mitral Stenosis and Insufficiency or Combined Valvular Disease

Age	Male		Female		Total	
	Total No. of patients	No. of embolic cases	Total No. of patients	No. of embolic cases	Total No. of patients	No. of embolic cases
~20 years	13	1	28	1	41	2
21~30	31	5	63	6	94	11
31~40	42	5	52	7	94	12
41~50	21	2	40	3	91	5
51~60	12	1	22	2	34	3
61~	4	2	2	0	6	2
Total	123	16	207	19	330	35

In Patients with S.B.E.

Age	Total No. of patients	No. of embolic cases
~20 years	7	1
21~30	25	4
31~40	18	2
41~50	7	1
51~60	8	2
61~	3	0
Total	68	10

on the patients with mitral and combined valvular disease. In these cases, the age distribution was peaked between the second and third decade in male and at the third decade in female. Daley and his co-workers,[17] however, demonstrated that the maximal incidence of cerebral embolism complicated with rheumatic heart disease was in the fourth decade. No attempt was made to explain this difference between the results of Daley's and ours.

The complication of cerebral embolism in the patients with S.B.E. had no relationship with their ages.

Time intervals between episodes of cerebral embolism—

The occurrence of one or more emboli within 24 hours was considered to be one episode, for it was difficult to recognize the recurrence of emboli in such a short period of time.

As shown in Table III, two-thirds of 56 patients had only one episode. Of 37 patients with valvular disease of the heart, 26 (70%) were cases of

Table III. Number of Embolic Episodes

No. of episode	M. S. M. S. I.	C. V. D.	A.	Total	H.C.V.D A.H.D.	Cong. H. D.	S. B. E.
1 Episode	17	7	2	26	5	1	6
2 Episodes	4	3		7	2	1	2
3 Episodes	2	1		3			2
4 Episodes	1			1			

Table IV. Time Interval between Episodes

	M. S. M. S. I.	C. V. D.	A.	H. C. V. D. A. H. D.	Cong. H. D.	S. B. E.
1 day ~ 1 week						1
1 week ~ 1 month	3	2				1
1 month ~ 6 months	2	1			1	2
6 months ~ 1 year	1					1
1 year ~ 5 years	2	2		2		
5 years ~ 10 years	1					
over 10 years	1					

single episode, and multiple emboli were observed in remaining 11 (30%) cases. In Daley's study,[17] the cases without recurrent episodes of emboli were 41%.

In the cases with two or more embolic episodes, the time interval between the episodes varied from several days to 10 years, however the intervals in about one half of the cases with multiple episodes were within 6 months (Table IV). This finding is well in accordance with that of Daley and his associates.[17]

Predisposing factors of cerebral embolism—

There have been postulated that atrial fibrillation, congestive heart failure, dilatation of the heart, digitalis therapy and others may be predisposing factors for the development of cerebral embolism.

Atrial fibrillation: In the present study consisting of 56 embolic patients, 29 had atrial fibrillation and 26 had sinus rhythm at the time of the episode. In valvular diseases of the heart, cerebral embolisms were found in 12.7% of patients with atrial fibrillation, but in only 5.8% with sinus rhythm (Table V). Similar results were found in hypertensive and sclerotic heart disease. The incidence of cerebral embolism was higher in cases with atrial fibrillation than that with sinus rhythm. On the contrary, all 11 cases of S.B.E. with embolic episode had sinus rhythm, and the result seemed to be indicating a specific behavior of S.B.E. in the cause of cerebral embolism.

Table V. Relationship between the Rhythm of the Heart and the Incidence of Cerebral Embolism

	Sinus rhythm		Atrial fibrillation	
	No. of patients	No. of embolic cases	No. of Patients	No. of embolic cases
M. I.	22	0	8	0
M. S., M. S. I.	81	7	110	16
C. V. D.	56	7	53	5
A.	84	0	10	2
Total	243	14 (5.8%)	181	23 (12.7%)
H. C. V. D. A. H. D.	245	2	58	5
Cong. H. D.	87	1	3	1
S. B. E.	65	10	3	0
Other	69	0	74	0

Table VI. Time Interval between the Embolic the Episode and the Onset of Atrial Fibrillation (28 cases)

Time interval	within 1 months	1~2 months	2~3 years	5~6 years	about 10 years	about 20 years	unknown
No. of cases	2	2	3	1	3	2	15

The duration of atrial fibrillation before the first embolic phenomenon in 13 patients was ranging from 2 to 20 years (Table VI), and the half of them was within 2 or 3 years. According to Harris,[18] the occurrence of cerebral embolism is most frequent within several weeks or months after the onset of atrial fibrillation. However, he also stated that some cases had embolic episode within a few hours to 2 days after the conversion to sinus rhythm from atrial fibrillation.

Heart size: It has been stated that cerebral embolism could occur even with sinus rhythm when there was the dilatation of the left atrium.[19] No such a correlation was found between the size of the heart and cerebral embolism in our series (Fig. 1), although we used cardio-pulmonary ratio for the determination of the cardiac size rather than the measurement of the left atrium. On the other hand, Daley and his co-workers[17] cited that the embolism was uncommon in patients with giant left atria.

Digitalis therapy and congestive failure (Table VII and VIII): At the time of embolic episode, 20 cases had been receiving some digitalis preparation, and remaining 36 had no digitalis. Thirty-two cases were in congestive failure at the time of embolic episode, and 24 were not in failure. From these data, no correlation can be found between cerebral embolism and digitalis therapy

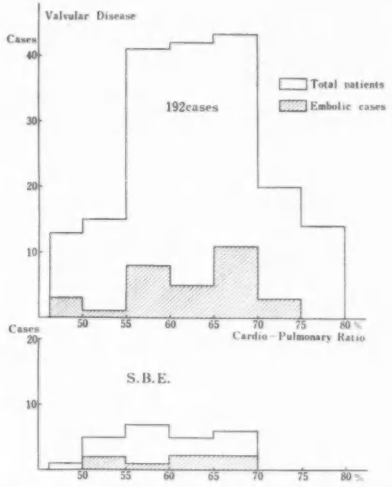

Fig. 1. Relationship between the cardio-pulmonary ratio and cerebral embolism.

Table VII. Relationship between the Administration of Digitalis and the Incidence of Cerebral Embolism

Total number	Digitalis used	Digitalis not used
56	20	36

Table VIII. Relationship between Congestive Heart Failure and Incidence of Cerebral Embolism

Total number	Congestive failure present	Congestive failure not present
56	32	24

and/or congestive heart failure. Harris[18] stated the same results. However, some other workers convinced that cerebral embolism often occurred in congestive failure, because of the retarded blood flow.[20][21]

Other factors predisposing cerebral embolism, such as administration of quinidin, exercise or postual change of the body are studied by some workers,[22]–[24] but they did not clarify and we also failed to demonstrate any definite correlation.

The neurological symptoms at the time of embolic episode—

In this paper, neurological symptoms were studied on 78 episodes of cerebral embolisms (Table IX). Paralysis was found in 59 (76%). There was no correlation between these symptoms and the nature of the heart disease.

Mental deterioration and death: In general, it has been known that the grade of mental deterioration was less in cerebral embolism than in cerebral hemorrhage,[1],[27] and this mental disturbance has been thought to have a close relationship with the prognosis of cerebral embolism.

Of 42 episodes with mental deterioration, 33 (77%) recovered from it,

Table IX. Neurological Symptoms of Cerebral Embolism (78 Episodes)

	MS., MSI. C.V.D.	A.	H. C. V. D. A. H. D.	Cong. H.D.	S.B.E.	Total
Mental deterioration	26	1	4	2	9	42
Disturbance of speach	28	1	6	3	7	45
Paralysis	39	1	7	3	9	59
Restlessness	4					4
Muscular rigidity	1					1
Convulsion	8				5	13
Sensory disturbance	6	1	4	1	3	15
Visual defect	1					1
Psychopathic symptom					1	1

Table X. Duration of the Survival and Mental Deterioration after Cerebral Embolism

	MS., MSI. C.V.D.		A.		H. C. V. D. A. H. D.		Cong. H.D.		S.B.E.	
	Death	Re-covery	Death	Re-covery	Death	Re-covery	Death	Re-covery	Death	Re-covery
Within 6 hours		11				1			1	3
6～12 hours	1									
12～24 hours	2	1						2	2	
1～ 2 days		5				1			1	
2～ 3 days		2				1				
3～ 4 days	1	1								
4～ 5 days		1							1	
5～ 7 days		1		1						
7～10 days										
over 10 days						1				1
Total	4	22	0	1	0	4	0	2	5	4

but 9 (21%) died without restoring the consciousness. Six deaths of the 9 cases occurred within 24 hours after the onset of symptom, and 18 of 33 survival cases restored the consciousness within 24 hours (Table X). According to Newbill,[25] however, only 1 case of 19 deaths by cerebral embolism died in 24 hours, and 10 cases between 6 and 15 days, and Mohr[25] also stated that

few died in 6 days after embolic episode.

Paralysis and disturbance of speech: Of 59 paralytic cases, right-sided hemiplegia* was 33 and left-sided was 26. This data did not demonstrate the strong predominance of one side as well as previous reports by Keen[3] and Popper[1] (Table XI). Some authors believed that emboli traveled with

Table XI. Relationship between the Disturbance of Speech and Side of Hemiplegia

	Aphasia	Dysarthria	Not diagnosed	No disturbance	Total
Right-sided hemiplegia	11	5	8	9	33
Left-sided hemiplegia	1	9	6	10	26
No hemiplegia	2	1	2		5
Total	14	15	16	19	64

greater facility in the right than in left carotid arteries, as might be expected from the anatomy of the aortic arch,[17),26)] but other workers objected to this opinion and, in fact, they found that the left hemisphere was more frequently involved than the right.[28)]

Of 33 cases with right hemiplegia, 24 (73%) had disturbance of speech, and 16 (62%) of 26 cases of left hemiplegia had the same disturbance. These results seem to agree with the thought that the left hemisphere has the superiority concerning the speech. Of 45 disturbances of speech, 14 were aphasia and 15 were dysarthria.

Table XII. Status of Recovery from Paralysis after Cerebral Embolism (42 episodes)

	M.S., MSI. C.V.D.	A.	H.C.V.D. A.H.D.	S.B.E.	Total
Complete	10	0	1	1	31
Moderate	12	0	5	2	
Poor	7	1	1	2	11

Convalescent study of paralysis was made on 42 cases (Table XII), and a total of 31 cases (74%) recovered from the paralysis, of which complete recovery was found in 12 and moderate (no interference in daily life to certain extent) in 19. These results indicate that the improvement of paralysis after cerebral embolism is relatively fair, in spite of the previous report stating that the repair of the lesion of cerebral embolism is slower than that of hemorrhage.[29)] The results in the present study are well agreed by the findings of Keen

* Throughout this manuscript, the term of " Hemiplegia " is used to include hemiparesis.

and Leveaux[3] and Sassa.[30]

Postmortem Data—

Fifty-five patients with various types of cardiac disease were autopsied, and their brains were examined. Of these 55 cases, 17 cases (31%) complicated the cerebral embolism (Table XIII). In this group 38% of valvular diseases and 70% of S.B.E. had embolic findings in the brain.

Table XIII. Incidence of Cerebral Embolism in Autopsied Cases of Cardiac Disease

	No. of autopsies	No. of embolic cases	%
M.S., M.S.I., C.V.D.	24	9	38
A.	7	1	14
H.C.V.D., A.H.D.	14	0	0
S.B.E.	10	7	70
Total	55	17	31

Table XIV. Incidence of Emboli in the Various Organs

	Brain	Arachnoidea	Lung	Spleen	Kidney	Mesentery
M.S., M.S.I. C.V.D. (24 cases)	9	0	8	5	7	1
S.B.E. (10 cases)	7	5	2	4	6	0

Incidence of embolism in the brain and other organs: Of 24 patients with mitral and combined valvular disease, 9 had cerebral, 8 had pulmonary and 7 had renal embolism (Table XIV). Of 10 patients with S.B.E., 7 had cerebral, 5 had arachnoidal and 4 had splenic embolism. These data agreed with the results of other workers who stated that cerebral embolism was more frequent than that of other organs in rheumatic heart disease,[2][4][17] nevertheless embolism of the spleen or kidney was more frequent than the brain in S.B.E.[7]

Intracardiac mural thrombi: In patients with mitral and combined valvular disease, 6 (60%) of 10 cases with intracardiac mural thrombi had clinical embolic episode, and in 25 cases without mural thrombi, only 4 (16%) had cerebral embolism. However, in S.B.E. 4 (50%) of 8 cases without mural thrombi had embolic episode (Table XV).

Pathological diagnosis of cerebral embolism was made in 6 (86%) of 7 cases with mural thrombi and 3 (18%) of the 17 cases without them (Table XVI). These results in this study are in accordance with previous reports.[9][31]

From these findings, it is clear that mural thrombosis plays an important

Table XV. Relationship between Mural Thrombi in Left Heart and Clinical Cerebral Embolism

M.S., M.S.I., C.V.D.				S. B. E.			
With mural thrombi in the left heart		Without mural thrombi in the left heart		With mural thrombi in the left heart		Without mural thrombi in the left heart	
10		25		7		8	
Embolic episode	No embolic episode	Embolic episode	No embolic episode	Embolic episode	No embolic episode	Embolic episode	No embolic episode
6 (60%)	4 (40%)	4 (16%)	21 (84%)	2 (29%)	5 (71%)	4 (50%)	4 (50%)

Table XVI. Relationship between Mural Thrombi in Left Heart and Pathological Findings of Cerebral Embolism

M.S., M.S.I., C.V.D.				S. B. E.			
With mural thrombi in th left heart		Without mural thrombi in th left heart		With mural thrombi in the left heart		Without mural thrombi in the left heart	
7		17		5		4	
Embolic findings in brain	No embolic findings in brain	Embolic findings in brain	No embolic findings in brain	Embolic findings in brain	No embolic findings in brain	Embolic findings in brain	No embolic findings in brain
6 (86%)	1 (14%)	3 (18%)	14 (82%)	2 (40%)	3 (60%)	2 (50%)	2 (50%)

Table XVII. The Location of the Lesion in Cerebral Embolism

	Cerebral cortex	Basal ganglia+ Internal capsule	Arachnoidea	Brain stem	Cerebellum
M.S., M.S.I., C.V.D.	3	12	0	1	1
A.	1	1	0	0	0
S.B.E.	4	4	5	0	0
Total	8	17	5	1	1

role in the occurrence of cerebral embolism in the patients with valvular diseases of the heart.

Locations of the cerebral embolism: It has been known that the embolus dislodged from fibrillating left atrium is usually large, and occludes the main artery such as the middle cerebral artery, but that in S.B.E. many small emboli lodge in narrower arteries.[32] As shown in Table XVII, 12 of 17 cases of valvular disease of the heart had the lesion in basal ganglia and internal capsule. On the other hand, cerebral embolisms caused by S.B.E. were evenly distributed in cerebral cortex, basal ganglia or internal capsule and arach-

Table XVIII. The Location of Involved Artery in Cerebral Embolism

	Chorioidal artery	Cerebral artery			Branch of basilar artery
		Anterior	Middle	Posterior	
M.S., M.S.I., C.V.D.	0	0	13	2	2
A.	1	0	1	0	0
S.B.E.	0	1	7	0	0
Total	1	1	21	2	2

Table XIX. The Laterality of the Lesion of Cerebral Embolism in Autopsied Cases

	Right-sided cerebrum	Left-sided cerebrum	Arachnoidea	Total
M.S., M.S.I., C.V.D.	8	7	0	15
S.B.E.	2	6	5	13

noidea. The middle cerebral artery were occluded in 21 (78%) of 27 cases (Table XVIII). This finding is essentially the same as that of Popper[1] and others.[26)33)34)]

The lesion in the brain were left-sided in 10, and right-sided in 13 which were well correlated with clinical findings (Table XIX).

The results in this study together with that of Hall[33] seem to indicate that no laterality of cerebral embolic lesion exists.

Summary and Conclusion

(1) Clinical and pathological findings were studied in 56 cases of cerebral embolism among 1,029 patients admitted to the Second Medical Department, Tokyo University Hospital from 1941 to 1957.

(2) No sexual difference was found (male 30, female 26).

(3) The nature of the underlying heart diseases were as follows; mitral stenosis, mitral stenosis and insufficiency, combined valvular disease, sclerotic and hypertensive heart disease, congenital heart disease, S.B.E., and so on.

(4) Thirty per cents of 56 cases had multiple embolic episodes. Interval between each episode was within 6 months in about one half of the cases.

(5) It was demonstrated that atrial fibrillation was the very important factor as the cause of emboli, and digitalis therapy, congestive failure or size of the heart were not related to the occurrence of cerebral emboli.

(6) Paralysis was the most frequent neurological symptom. No dominant laterality was found. Recoveries from paralysis were complete or

moderate in 74%.

(7) Recovery from mental deterioration was seen in 79%, one half of which restored the consciousness in 24 hours.

(8) Many cerebral embolic episodes occurred in valvular heart disease with intracardiac thrombus. On the other hand, many cases of S.B.E. without intracardiac thrombus developed cerebral emboli.

(9) The lesions of basal ganglia and internal capsule were found to be most frequent, and the area of middle cerebral artery was involved far more frequently than the other area.

References

1. Popper, L.: Wien Zeitschrift f. Inn. Med. **30**: 1, 1949.
2. Wood, P.: Brit. Med. J. **12**: 263, 1950.
3. Keen, G. and Leveaux, V. M.: Brit. Med. J. **5088**: 91, 1958.
4. Weiss, S. and Davis, D.: Am. Heart. J. **9**: 45, 1933.
5. Mikata, I.: Saishin-igaku **9**: 1955, 1954 (In Japanese).
6. Clawson, B. J.: Arch. Int. Med. **33**: 157, 1924.
7. Morgan, W. L. and Bland, E. F.: Circulation **19**: 753, 1959.
8. Jordan, R. A., Scheifley, C. H., and Edward, J. E.: Circulation **3**: 363, 1951.
9. Bean, W. B. and Spadin, A.: Am. J. Med. **7**: 765, 1949.
10. Bean, W. B. and Read, C. T.: Am. Heart. J. **23**: 362, 1942.
11. Söderström, N.: Acta Med. Scandinav. Suppl.: 217, 1948.
12. Miller, R. D., Jordan, R. A., Parker R. L., and Edward, J. E.: Circulation **6**: 7, 1952.
13. Doscher, N. and Poindexter, C. A.: Am. J. Med. **8**: 623, 1950.
14. Harvey, J. C.: Ann. Int. Med. **47**: 1067, 1957.
15. Gleason, I. O.: Cancer **8**: 839, 1955.
16. Straus, R. and Merliss, R.: Arch. Path. **39**: 74, 1945.
17. Daley, R., Holt, C. L., Bland E. F., and White, P. D.: Am. Heart J. **42**: 566, 1951.
18. Harris, A. W. and Levine, S. A.: Ann. Int. Med. **15**: 637, 1941.
19. Friedberg, C. K.: Disease of the Heart (2nd ed.), W. B. Sounders Co., Philadelphia, p. 362, 1956.
20. Garvin, C. F.: Am. Heart. J. **21**: 213, 1941.
21. Jordan, R. A., Miller, R. D., Edward J. E., and Parker, R. L.: Circulation **6**: 1, 1952.
22. Goldman, M. J.: Am. Heart J. **40**: 93, 1950.
23. Sokolow, M. and Edgar, A. L.: Circulation **1**: 576, 1950.
24. Burne, G.: Brit. Heart J. **12**: 263, 1950.
25. Newbill, H. P.: J.A.M.A. **114**: 236, 1940.
26. Mohr, L. and Staehelin, R.: Handbuch der Inn. Med., Springer-Verlag, Berlin, V. (3): 55, 1953.
27. Okinaka, S.: No no Kekkanshogai (Cerebral Vascular Diseases) Saishin-igaku, Osaka, p. 47, 1955 (In Japanese).
28. Ask-Upmark, E.: Acta Med. Scandinav. **152**: 433, 1955.
29. Okinaka, S.: Naika **1**: 266, 1958 (In Japanese).

30. Sassa, R.: Juyonaru Shikkan no Yogo (Prognosis of Important Diseases), Shindan to Chiryosha, Osaka, p. 132, 1939 (In Japanese).
31. Willius, F. A.: Am. J. Med. Sc., **171**: 48, 1926.
32. Grinker, R. R. and Bucy, P. C.: Neurology (4th ed.), C. C. Thomas, Springfield, p. 512, 1949.
33. Hall, P., Denker, S. J., and Biörck, G.: Am. Heart. J. **44**: 600, 1952.
34. Baker, A. B.: Clinical Neurology, Hobber-Harrer New York, **1**: 507, 1955.

Rheumatic Fever in Children—A Statistical Report in Japan

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Masao IIJIMA, M.D., *and* Yoshiro OBE, M.D.

A statistical observation was made over 184 cases of rheumatic fever in children at the Pediatric Clinic of Tokyo University Hospital. The number of patients with rheumatic fever has been increased recently in Japan. The disease occur most often in spring and autumn, and the first attack is most commonly encountered between the age of 5 and 12 years. Nineteen per cent of the patients with rheumatic carditis had insidious onset. This type of carditis has a clinical importance because of its high incidence of residual cardiac damage.

RHEUMATIC fever is one of the most important diseases in children because of its serious complication, i.e. carditis. The number of the patients with rheumatic fever has been reported to be decreasing in the United States and Europe in recent years, but contrarily in Japan its incidence has been increasing. In order to make a statistical analysis of this disease the present study was undertaken.

Materials and Methods

One hundred and eighty four cases of rheumatic fever were observed from Jan. 1949 to Dec. 1957 at the Pediatric Clinic of Tokyo University Hospital. All cases had diagnostic criteria of rheumatic fever by Jones.

Results

Incidence—

The number of cases, which were observed at the Pediatric Clinic of Tokyo University Hospital, appeared to be increasing year after year since 1949. The ratio between rheumatic cases and the total number of patients admitted to the hospital has also been increased (Fig. 1).

Seasonal Incidence:

The monthly incidence of rheumatic patients was as in Fig. 2. Greater number of rheumatic cases were observed in October, November, December and March, April and May, and the prevalence in autumn and spring was shown.

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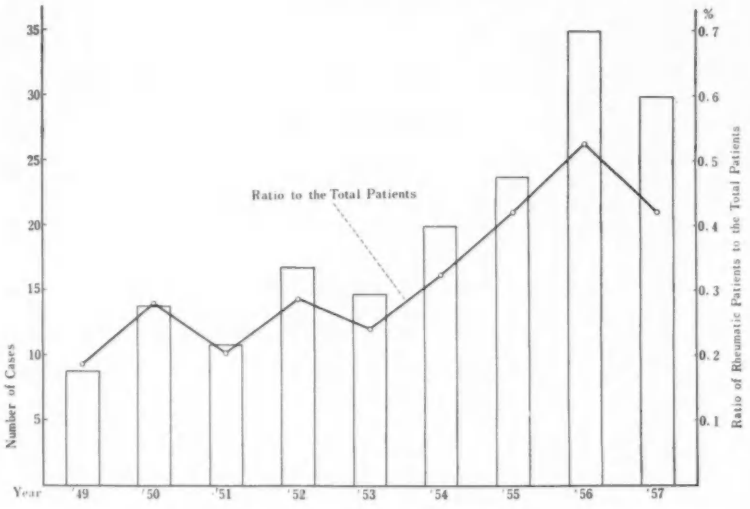

Fig. 1. Annual incidence of rheumatic fever.

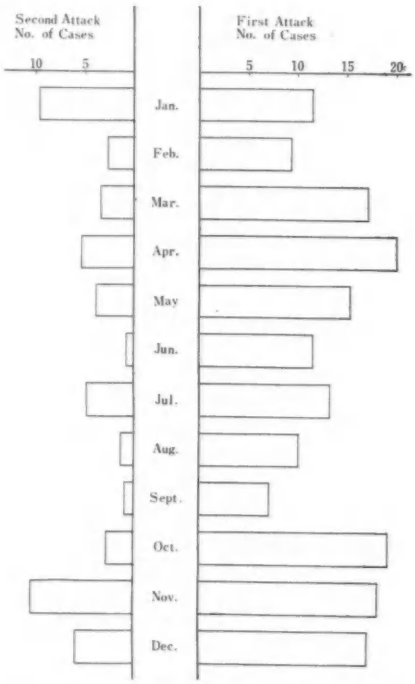

Fig. 2. Seasonal incidence of rheumatic fever.

Ages at Onset and Sexual Incidence:

The first attack commonly occurred between the age of 5 and 12, with the peak at 7 years of age. The second attack was between 9 and 11 years of age (Fig. 3). A total of 101 cases was male (54.9%) and 83 cases female (45.1%).

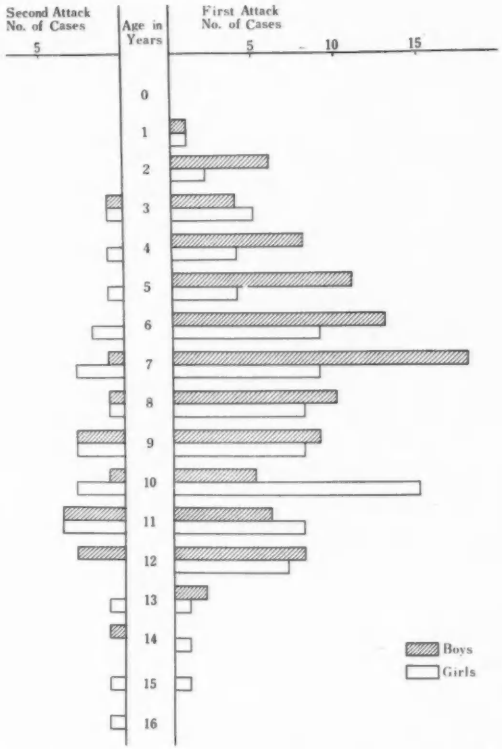

Fig. 3. Age at the onset and sexual incidence of rheumatic fever.

Symptoms—

Incidence of each major manifestation:

The incidence of each major manifestation is seen in Table I. Carditis was found in 99 cases (54.7%), and polyarthritis was encountered in 125 cases (82.7%).

Carditis:

Of all 99 cases with rheumatic carditis, 7 cases were accompanied by pericarditis, and 33 cases (33%) by congestive failure. In 19 cases, carditis occurred insidiously, without any acute manifestations such as high fever and/or polyarthritis. In these cases, however, some abnormal laboratory findings,

Table I. Incidence of Rheumatic Manifestations

Major manifestation			
Carditis	54.7%	Subcutaneous nodules	8.9%
Polyarthritis	82.3%	Erythema marginatum	7.7%
Chorea minor	10.3%		
Minor manifestations and other symptoms			
Fever {high degree / low grade}	84.9% {69.1% / 15.8%}		
Elevated ASL-O value	70.3%	Abdominal pain	15.0%
Positive culture of strept. hem.	25.8%	Changes in ECG	59.8%
Increased ESR	90.9%	History of rheumatic fever	25.0%
Epistaxis	15.5%		

such as increased erythrocyte sedimentation rate, elevated ASL-O value and slight degree of arthralgia etc., were present. In such cases, the occurrence of carditis was often overlooked for a long time, and the delayed administration of steroid hormone often resulted in a residual valvular disease. The results of laboratory examinations in such a case were shown in Table II. High clinical significance was considered in these cases because of a greater incidence of residual cardiac damage.

Table II. Laboratory Findings in Rheumatic Carditis with Insidious Onset

	Positive cases	Total cases	per cent
Increased ESR	13	13	100
Elevated ASL-O	4	5	80
Changes in ECG	5	7	71
Slight arthralgia	9	16	56
Epistaxis	5	14	36
Low grade fever	2	19	10

Polyarthritis:

The incidence of arthritis in each joint is seen in Table III. Most frequently the knee joint was involved, and the arthralgia was often migratory type. Swelling of the affected joint was found in 44.3% of all the cases with polyarthritis.

Table III. Incidence of Arthritis in Each Joint (73 cases)

Neck	5.5%	Finger	5.5%
Shoulder	8.2%	Hip	16.4%
Elbow	23.3%	Knee	60.3%
Wrist	33.0%	Ankle	52.0%

Chorea:

Only in the cases with chorea, the diagnostic criteria of Jones was fullfilled. The occurrence of other rheumatic manifestations in chorea is presented in Table IV, such as carditis, polyarthritis and fever. In general, they

occurred less frequently in comparison to those in rheumatic fever.

Table IV. Incidence of Rheumatic Symptoms Accompanied by Chorea (19 cases)

Carditis	42.1%	Fever	72.2%
Nodules	5.6%	Increased ESR	43.8%
Polyarthritis	61.1%		

Incidence of each minor manifestation:

As shown in Table I, increased erythrocyte sedimentation rate and fever were most commonly observed.

Fever:

The remittent type of fever was most prevalent and 53.6% of cases had temperature over 39°C (Table V). Though the duration of fever was variable, almost all cases showed abrupt fall of high temperature to the normal level in a few days after the start of the hormone therapy.

Table V. Duration and Degree of Fever in Rheumatic Fever (84 cases)

Degree of fever	No. of cases	per cent	Duration	
below 37.5°C	12	14.3		
37.5°~37.9°C	4	4.8	within 2 weeks 2~6 weeks more than 6 weeks	2 0 2
38°~38.9°C	23	27.4	within 2 weeks 2~6 weeks more than 6 weeks	18 5 0
over 39°C	45	53.6	within 2 weeks 2~6 weeks more than 6 weeks	30 12 3

ASL-O level:

In a total of 184 cases studied, 70.3% showed an elevation of ASL-O level.

Erythrocyte sedimentation rate:

The majority of the cases showed an elevated erythrocyte sedimentation rate more than 60 mm. per hour, and 22% of the cases over 100 mm. Fifteen cases, in which erythrocyte sedimentation rate was not increased, consisted of 7 cases of chorea minor and 7 with congestive failure.

White blood cell count:

The majority (58.3%) of the cases showed leucocytosis more than 10,000 /mm^3. The correlation between the leucocyte count and the shift to the left is as in Table VI.

Red blood cell count:

Table VI. White Blood Cell Count and Shift to the Left in Rheumatic Fever (108 cases)

		White blood cell count						Total	%
		～6,000	6,001～8,000	8,001～10,000	10,001～12,000	12,001～15,000	15,000～		
% of band cell	0～9	5	11	15	14	13	7	65	60.2
	10～15	1	5	2	4	2	5	19	17.6
	16～20	1	2	2	2	3	1	11	10.2
	21～	0	1	0	3	2	7	13	12.0
Total		7	19	19	23	20	20	108	
%		6.5	17.6	17.6	21.3	18.5	18.5		100.0

While the appearance of rheumatic patient is pale, only 17.3% of all cases showed the true anemia under 3.5 millions per mm.^{3} The cases which showed the anemia under 2 millions per mm.^{3} had episodes of severe epistaxis.

Prognosis—

Only the cases with more than a year follow up and those without prophylactic measure of rheumatic fever were subjected to the present study. Since most of these patients were studied before 1955, they had not received sufficient hormone therapy. These cases were divided into two groups according to the presence or absence of carditis. Among a total of 83 cases studied, there were 62 cases with carditis and 21 without carditis. A total mortality rate was 16.9% (14 cases), and the mortality rate of the group without carditis was zero. Overall recurrence rate was 55.3% (43 cases), and each recurrence rate was 58.9% in the cases with carditis and 47.6% in the group without carditis at the initial attack, and this difference between both groups was not statistically significant.

Discussion

It has been known that rheumatic fever was the most important cause of the valvular disease of the heart, and the majority of acquired valvular heart disease in childhood was due to rheumatic in origin. It is said that in the United States and Europe rheumatic fever has been decreasing in number recently, however, the result of the present study indicated the increasing incidence of rheumatic fever in Japan.

Since the introduction of steroid hormone in the treatment of rheumatic fever, rheumatic carditis has become curable. Needless to say, the early diagnosis and the early treatment with hormone are essential for a successful treatment of rheumatic fever and this leaves no residual cardiac damages. Therefore, the recognition of signs of rheumatic fever is necessary for the early diagnosis of rheumatic fever, and it is not difficult to make a diagnosis of rheumatic fever when it is fullblown cases.

On the other hand, the insidious onset of rheumatic carditis has a great

clinical importance, since such a carditis is apt to be overlooked at the onset of the disease with vague symptoms. This causes the delay in the introduction of hormone therapy, and the residual cardiac damage is often persistent. In such a case, however, abnormal laboratory findings such as ASL-O and erythrocyte sedimentation rate will be of great value in suspecting rheumatic carditis.

Then, it is concluded that when rheumatic carditis is suspected a prompt and a massive hormone therapy should be considered in diminishing the degree of the residual cardiac damage or even in bringing a permanent cure. The emphasis should be given to an early diagnosis and early treatment of such an insidious type of rheumatic carditis, and it is one of the important problems in the field of pediatric medicine.

As for the prognosis of rheumatic fever, there were reports by Bland and Jones,[1] McCue,[2] Wilson[3] and Ash.[4] Their studies have been done before the so-called steroid era, and the course of rheumatic fever in their cases was considered as natural and unmodified by the hormone therapy. Bland and Jones reported the results of their observation of 1,000 rheumatic cases over 20 years period. According to their reports, one fifth of the cases were dead within 10 years after the initial attack, and 30% of the cases were dead within 20 years, and one third of total death occurred in the first five years. The rate of recurrence of rheumatic fever is about one fifth in the first 5 years, one tenth in the subsequent 5 years, and one fifteenth in following each 5 years. Wilson reported that the total mortality rate of rheumatic patients was 147 per one thousand. McCue observed one recurrence or more in 61% of their 504 cases of rheumatic fever, and cardiac involvement in 83% and death in 7.1%. The results of the present study are in accordance with these reports.

Although the majority of cases in this study was observed between 1949 and 1957, the prognosis and the recurrence rate were studied mainly in cases of between 1949 and 1955. Before 1955, therapy with massive doses of steroid hormone and the prophylaxis of recurrence of rheumatic fever were not prevailed in Japan. Therefore, the authors' results are considered to show a natural course of rheumatic fever in Japan.

Summary

During the year of 1949 till 1957, a total of 199 attacks in 184 cases of rheumatic fever in children were observed at the Pediatric Clinic of Tokyo University Hospital. It appeared that recent increase of rheumatic patients was observed in Japan. According to the statistical analysis of the disease, it occurred particularly in March, April and October, November and December. The first attack was most common between the age of 5 and 12, and 80% of the total cases were fallen in this age group.

Carditis was observed in 54.7%, and polyarthritis in 82.3% of the total cases. As to the minor manifestations, high fever was found in 69.1% and increased erythrocyte sedimentation rate in 90.9%. Among the cases of rheumatic

carditis, 19% of the cases showed an insidious or latent onset. Even in such cases, elevated antistreptolysin-O titer and increased erythrocyte sedimentation rate were found. Such a form of carditis was considered to have a great clinical significance because of its high incidence of residual cardiac damage.

A total of 83 cases of rheumatic fever was observed for more than 1 year without prophylactic measures for the recurrence of rheumatic fever. Among these, 14 cases (16.9%) died in the observation period. All these cases had carditis at their first attack. Recurrence rate during observation period was 22.6%, and one half of the recurrences occurred within the first year after the initial attack.

Importance of an early diagnosis of the disease and a prompt therapy was emphasized.

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References

1. Bland, E. F. and Jones, T. D. : Ann. Int. Med. **37** : 1006, 1952.
2. McCue, C. M. and Galvin, L. F. : J. Pediat. **33** : 467, 1948.
3. Wilson, M. G. and Lubschez, R. : J.A.M.A. **138** : 794, 1948.
4. Ash, R. : Am. Heart J. **36** : 89, 1948.

Studies on Myocardial Metabolism by Coronary Sinus Catheterization in Man—Relationship of Myocardial Metabolism to ECG and Cardiac Size

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The results concerning myocardial oxygen and carbohydrate metabolism obtained by coronary sinus catheterization were compared with electrocardiographic and X-ray findings in 158 cases. There was a significant decrease in myocardial citrate extraction in cases with ST-T abnormalities and a tendency of increase in myocardial oxygen extraction coefficient especially in cases of valvular heart disease with ST-T changes. QT_c and the magnitude of $\bar{G}$ correlated with oxygen extraction coefficient.

The difference in the relationship of myocardial metabolism to electrocardiogram and cardiac size in the different types of cardiac disease such as valvular, hypertensive and/or sclerotic disease of the heart was discussed.

IT has been difficult to analyse the relation of myocardial metabolism to electrocardiographic and X-ray findings. In recent years, several reports concerning the influence of alteration of various substrates upon myocardial membrane potential have been published.[1)-9)] From these observations, it was indicated that some electrolytes were essential for the electrical phenomenon associated with cellular activation of heart muscle, but the role of other substrates yet remains obscure. Moreover, a few previous reports obtained about electrocardiographic changes associated with oxygen deficiency did not directly concern myocardial metabolism.[10)–15)]

The results obtained by the method of coronary sinus catheterization may permit to presume the process of myocardial metabolism in human subjects, although the observation by this procedure is confined to myocardial extraction of various substrates.[16)–23)] By analysing the correlations of these data to electrocardiographic and X-ray findings, it is likely to be possible to surmise the relationships of myocardial metabolism to electrocardiogram and cardiac size.

The present paper is concerned with such analysis based upon the results

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obtained by the method of coronary sinus catheterization in man at the Second Department of Internal Medicine, Faculty of Medicine, University of Tokyo since 1952. Though we realize that the results of myocardial metabolic studies in this series are not adequate to make any conclusion concerning the relationships of myocardial metabolism to elctrocardiogram and cardiac size since they are limitted to those of myocardial gaseous and carbohydrate metabolism, an attempt was made to obtain some clue to clarify the present subject.

Materials and Methods

In 158 cases, the results of myocardial oxygen, glucose, lactate, pyruvate and citrate extraction obtained by the coronary sinus catheterization method were compared with the electrocardiographic and X-ray findings of the heart. The material was composed of the following groups: 30 normal subjects; 47 patients with various valvular heart diseases, including 20 mitral, 7 aortic and 20 combined valvular disease; 64 patients with hypertension and/or coronary sclerosis; 10 cases with thyrotoxicosis; 7 patients with anemia. The majority of cases with valvular disease suffered more or less from congestive heart failure.

The methods used for the determination of substrates and the appraisal of the results of myocardial metabolism were described in the previous papers.[20),24)-30)]

Electrocardiographic findings were obtained mostly from conventional 12 leads. In order to analyse the relationship between ECG and myocardial metabolism, the following portions of ECG were measured. They are the QRS, ST, T, QT and ventricular gradient in frontal plane ($\hat{G}$). The methods of classification of these are to be described later.

For quantitative expression of cardiac size, the area of cardiac silhouette was measured by Ungerleider's formula on roentgenogram of chest or fluoroscopic figure, taken prior to coronary sinus catheterization, and its ratio to predicted area based on calculation from height and body weight was obtained. In addition, cardiothoracic ratio was measured simultaneously. Fluoroscopic figures were corrected in accordance with distance between X-ray tube and fluorescent plate.

Results

Myocardial oxygen, glucose, lactate, pyruvate and citrate metabolism—

The results of myocardial gaseous and carbohydrate metabolism were published previously in several papers.[20),24)-30)] In general, the extraction of these substrates was summarized as follows.

1) Oxygen: Coronary arterio-venous oxygen difference increased with arterial oxygen level in normal subjects. The normal range of myocardial oxygen extraction coefficient $(C_{AO_2}-C_{SO_2})/C_{AO_2}$ was 0.6 ± 0.1.

2) Glucose: Myocardial extraction of glucose seemed to be a function of arterial glucose concentration at the level of 80—100 mg./100 ml., but this relation in abnormal hearts did not differ definitely from that of normal.[29)]

3) Lactate and Pyruvate: On myocardial extraction of lactate and pyruvate, the following empirical formulae were obtained respectively.[25),26)]

$L_A = 0.116\ \Delta L^2 + 0.608\ \Delta L + 3.15$

L_A : arterial lactate concentration

ΔL : coronary arterio-venous lactate difference

$\Delta P = 0.75\ P_A - 0.34$

P_A : arterial pyruvate concentration

ΔP : coronary arterio-venous pyruvate difference

When myocardial metabolism of lactate or pyruvate was disturbed, the above-mentioned relationships varied respectively. For simplicity, it is possible to use the ratio of coronary arterio-venous lactate (pyruvate) difference to its normal mean value (extraction coefficient ratio) as a quantitative index of the disturbance. The ratio ranged from 70 to 120% in normal subjects and decrease in this ratio meant metabolic disturbance.

4) Citrate: The relationship between coronary arterio-venous citrate difference and arterial citrate concentration was as follows.[30]

$0.56\ C_A = \Delta C + 0.27$

C_A : arterial citrate concentration

ΔC : coronary arterio-venous citrate difference

In order to represent the degree of the metabolic disturbance, it is appropriate to use $C_S - 0.27/C_A$ or C_S/C_A (C_S : coronary venous citrate concentration). When myocardial citrate extraction decreases or becomes negative, their value increases.

Above-mentioned results were compared with electrocardiographic and roentgenologic findings.

Relationship between myocardial metabolism and ECG—

1) ST–T

The most frequent and important ECG findings, ST depression and T change, may appear as a result of various causes. Among them, coronary insufficiency and ventricular hypertrophy were most common in the present study. Since it is difficult to classify ST–T changes morphologically according to their causes, the subjects were divided into following three groups: cases without ST–T abnormality in limb and left precordial leads (ST–T (−)); cases with ST depression less than 0.05 mV. and/or flattening of T in more than one lead (ST–T (+)); and cases with ST depression more than 0.05 mV. and T change (ST–T (±)). Cases with inversion of T were included in the third group irrespective of existence of ST depression. No cases showed ST elevation.

Because of the difficulties in presuming the existence of coronary sclerosis by ECG in patients with hypertension, the cases with hypertension and/or coronary sclerosis were classified into following three groups. First, cases with hypertension but without ST–T change; second, cases with hypertension sion and ST–T changes; and third, cases without hypertension but with ST–T abnormalities.

After the above classification was made, a comparison study of metabolism and ST–T findings was carried out. Relation between oxygen extraction

coefficient ($\Delta 0_2/0_{2A}$) and ST–T change was shown in Fig. 1. In cases with ST–T change, oxygen extraction coefficient tended to increase. This tendency was definite in patients with valvular and hypertensive and/or sclerotic heart disease, excepting a few cases in each group. Increased oxygen extaction coefficient indicates that oxygen supply is insufficient to meet myocardial oxygen demand. This results from the relative deficiency of coronary blood flow. In other words, myocardium is in hypoxic state.

Myocardial glucose extraction did not correlate to ST–T findings. In patients with marked ST–T abnormalities, myocardial lactate and pyruvate metabolism was often disturbed. This relationship was also found in hypertensives and/or sclerotics, and it did not differ from that of valvular heart disease (Fig. 2 and 3).

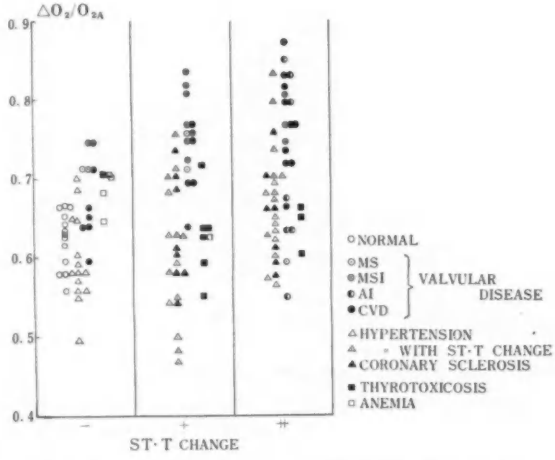

Fig. 1. Relation between myocardial oxygen extraction coefficient ($\Delta 0_2/0_{2A}$) and ST–T.

In many cases of valvular heart disease with ST–T changes, oxygen extraction coefficient is increased. Some patients with mitral stenosis show increased oxygen extraction coefficient in spite of absence of ST–T abnormality.

Myocardial citrate metabolism had close correlation with ST–T findings (Fig. 4). This corresponds with the relationship between oxygen metabolism and ST–T change. As shown in Fig. 4, most cases with ST–T abnormalities indicated disturbance of citrate metabolism, on the other hand most cases without ST–T change showed normal citrate metabolism. One case among those with normal ST–T (symbolized by ▲) showed ST depression after exercise.

2) QRS

No conclusive relationship was obtained between myocardial metabolism and the amplitude of Rv_5, Sv_2 and Rv_5+Sv_1/Rv_1+Sv_5. No measurement of the duration of QRS deflections was made because of its uncertainty.

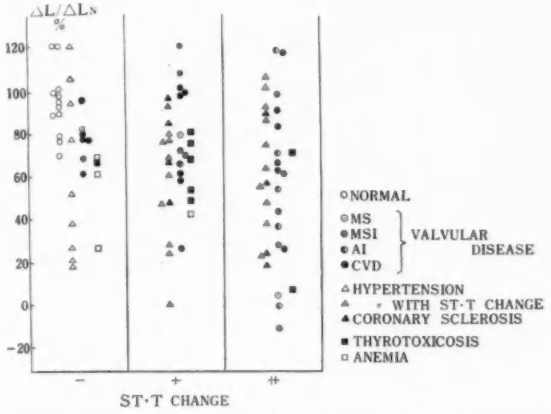

Fig. 2. Relation between myocardial lactate extraction coefficient ratio ($\Delta L/\Delta L_N$) and ST-T.
In cases with marked ST-T changes, $\Delta L/\Delta L_N$ is frequently decreased.

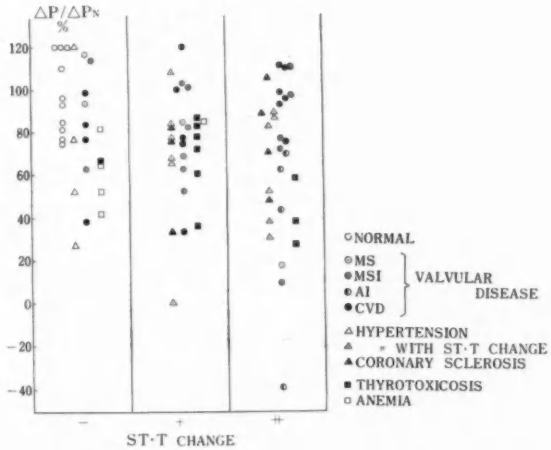

Fig. 3. Relation between myocardial pyruvate extraction coefficient ratio ($\Delta P/\Delta P_N$) and ST-T.
In patients with marked ST-T abnormalities, $\Delta P/\Delta P_N$ is often decreased.

3) QT

$QT/\sqrt{RR}$ (QTc) was used for the comparison because of variability of QT associated with RR. Cases with atrial fibrillation were excluded since it would be difficult to measure QTc accurately.

QTc has positive correlation with oxygen extraction coefficient (Fig. 5). In hypertensives and/or sclerotics, QTc occasionally increased to a greater extent than that of increase in oxygen extraction coefficient. This is perhaps

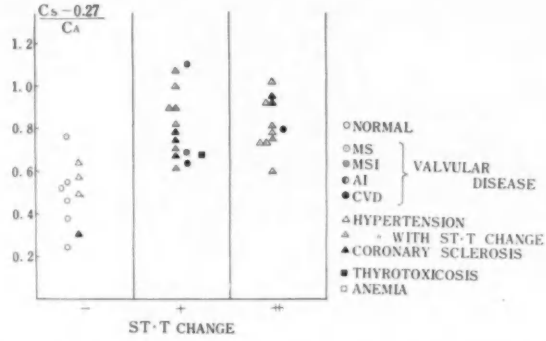

Fig. 4. Relation between myocardial citrate metabolism and ST-T.
Most cases with ST-T abnormalities indicate disturbance of citrate metabolism. In cases without ST-T change except one (▲), in which ST-T change appeared only after exercise, citrate metabolism was normal.

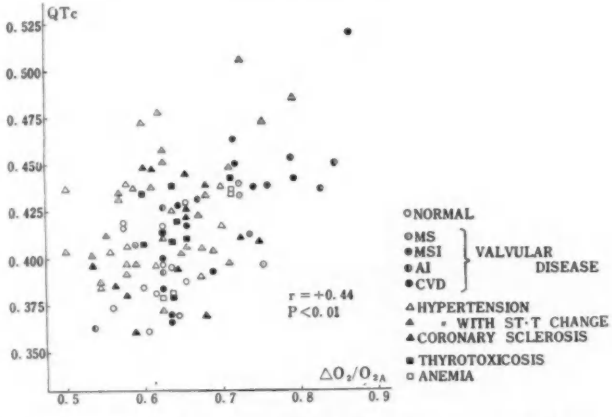

Fig. 5. Correlation of myocardial oxygen extraction coefficient ($\Delta 0_2/0_{2A}$) with QTc.

resulted from increase in cardiac work.[31),32)]

There was no definite correlation between coronary arterio-venous glucose difference and QTc.

Myocardial lactate, pyruvate and citrate metabolism also did not correlate with QTc significantly.

4) Ventricular Gradient ($\hat{G}$)

The magnitude of ventricular gradient in frontal plane correlated negatively with oxygen extraction coefficient (Fig. 6), but no evident relationship was obtained between the magnitude of $\hat{G}$ and myocardial glucose, lactate, pyruvate and citrate metabolism.

The direction of $\hat{G}$ and QRS-T angle appeared to be independent with

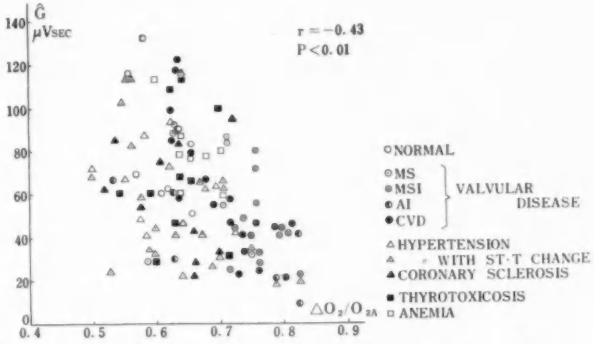

Fig. 6. Correlation between myocardial oxygen extraction coefficient ($\Delta 0_2/0_{2A}$) and the magnitude of Ĝ.

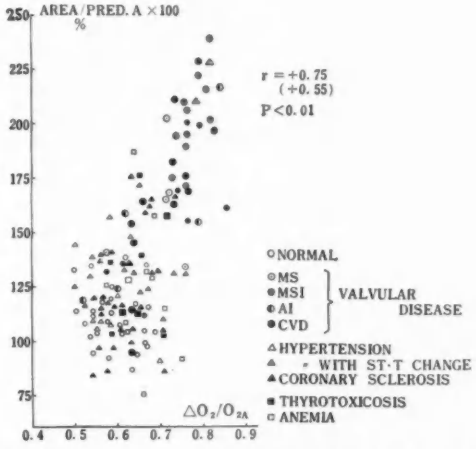

Fig. 7. Correlation of myocardial oxygen extraction coefficient ($\Delta 0_2/0_{2A}$) with cardiac area.

Larger dots represent cases in which cardiac area were measured by roentgenograms, and smaller dots by fluoroscopic figures. The coefficient of correlation concerns the results in cases in which the measurement of cardiac area was made by roentgenogram but that in the brackets does in all cases.

myocardial metabolism.

Relationship between myocardial metabolism and X-ray findings of the heart— The more the area of cardiac silhouette increased, the more the oxygen extraction coefficient augmented, especially in valvular disease of the heart (Fig. 7). This evident relation indicates that the cardiac enlargement will be associated with myocardial hypoxia. It is likely that oxygen consumption is more in enlarged heart than in the normal heart per the same weight of the myocardium. Regardless of the cause of the disease, every case with marked enlargement of the heart and the increased oxygen extraction coeffi-

cient suffered from clinical congestive heart failure. The previous reports[20),24-30)] indicated that myocardial hypoxia might be aggravated with the development of failure. It is therefore assumed that both myocardial hypoxia and cardiac enlargement increase in accord with the degree of heart failure.

A similar relationship was obtained between oxygen extraction coefficient and cardio-thoracic ratio (Fig. 8).

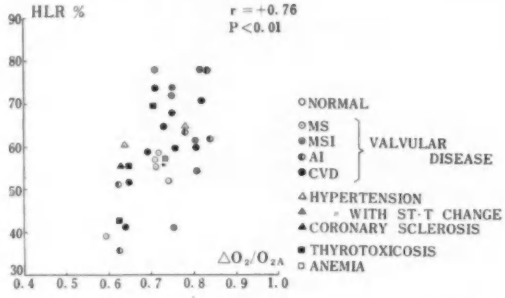

Fig. 8. Correlation between myocardial oxygen extraction coefficient ($\Delta 0_2/0_{2A}$) and cardio-thoracic ratio (HLR).
Measurement of HLR was made by roentgenogram in all cases.

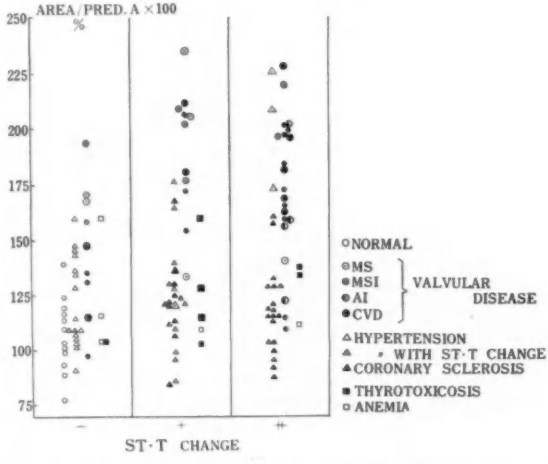

Fig. 9. Relation between ST-T and cardiac area. In cases represented by larger dots, cardiac area was measured by roentgenogram and in cases represented by smaller dots by fluoroscopic figure. In cases of valvular heart disease with ST-T changes, the heart tends to be enlarged.

Correlations between the area of cardiac silhouette and myocardial glucose, lactate and pyruvate metabolism were not apparent.

As the heart enlarged, myocardial citrate metabolism tended to be dis-

turbed, but this was not conclusive.

Relationship between ECG and cardiac size—

To evaluate correlation between myocardial metabolism and ECG or cardiac area it is essential to analyse the relationship between the latter two.

In cases of valvular disease of the heart in which ST–T change appeared, the heart tended to be enlarged. Occasionally marked enalrgement of the heart might be found among cases without ST–T abnormality, on the other hand, in some cases with marked ST–T change the cardiac size might not be so enlarged. The former was seen in patients with mitral stenosis, the latter aortic valvular disease with angina pectoris. In hypertensive and/or sclerotic

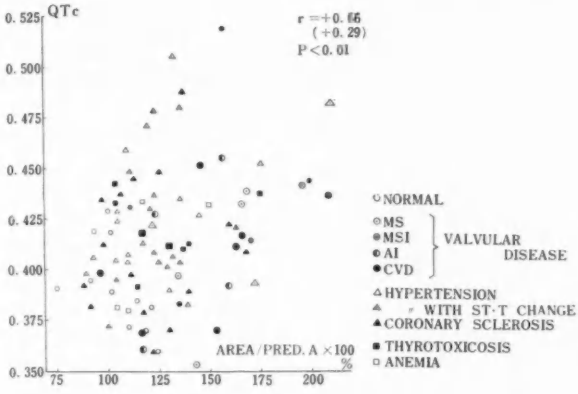

Fig. 10. Correlation of QTc with cardiac area. Sense of dots and prescription about the coefficient of correlation are similar as those of Fig. 7.

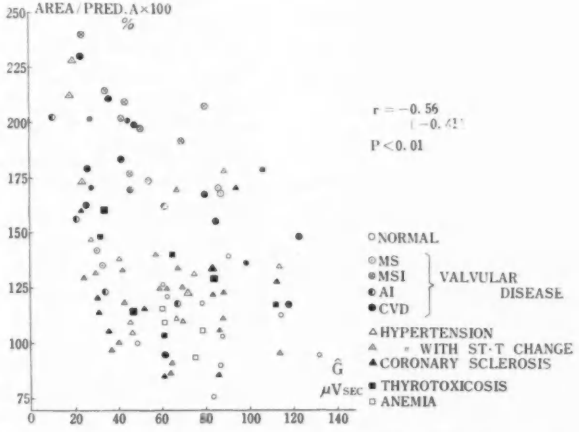

Fig. 11. Correlation between the magnitude of Ĝ and cardiac area. Sense of dots and prescription about the coefficient of correlation are similar as those of Fig. 7.

patients, relation between cardiac size and ST–T findings was not definite (Fig. 9).

QTc had slight but significant correlation with cardiac size. In hypertensives and/or sclerotics, the degree of increase in QTc seemed to exceed that of cardiac enlargement (Fig. 10).

Magnitude of $\hat{G}$ showed fair negative correlation with cardiac area (Fig. 11).

Discussion

As described above, the relationship among myocardial metabolism, ECG and X-ray findings in cases with valvular disease of the heart is somewhat different from that of hypertensives and/or sclerotics. It is therefore better to discuss the relation in these two groups separately. Above-mentioned relationships are summarized in Table I and II, in which the symbol of −, +, ++, +++, does not represent the degree of so-called correlation but the

Table I. Relations of Myocardial Metabolism with ECG and Cardiac Area

Metabolism→		Cases with valvular disease				Hypertensives and/or sclerotics			
		0_2	Lactate	Pyruvate	Citrate	0_2	Lactate	Pyruvate	Citrate
ECG	ST–T	++	+	+	(+)	++	+	+	+++
	QTc	+	±	±	(±)	++	±	±	(±)
	$\hat{G}$	+	−	−	−	++	−	−	−
Cardia area		+++	+	+	+	+∼++	−	−	+

Table II. Relation between ECG and Cardiac Area

ECG ↓ Cardiac area →	Cases with valvular disease	Hypertensives and/or sclerotics
ST–T	++	±∼+
QTc	+	++
$\hat{G}$	+	++

degree of influence of myocardial oxygen, lactate, pyruvate, glucose and citrate metabolism upon ECG and cardiac area on roentgenogram.

1) Valvular disease of the heart

There are the closest relation between oxygen metabolism and cardiac size. Each of ST–T, QTc and $\hat{G}$ has fair carrelation with myocardial oxygen extraction coefficent, and cardiac area also related to almost the same degree with ST–T. Comparing the relationship between ST–T and oxygen metabolism with that between ST–T and cardiac area, the latter seems to be

a little closer than the former. The relation between ST–T and myocardial oxygen metabolism appears to be secondary to the close relation between cardiac area and oxygen metabolism, although one cannot ignore the primary relation of the former.

QTc and $\hat{G}$ are also in similar condition to ST–T relating with myocardial metabolism and cardiac size.

So far as myocardial lactate and pyruvate metabolism is concerned, their relationship to ECG findings is less definite than the relationship to the cardiac size, suggesting that myocardial metabolism has influence indirectly upon ECG through cardiac size.

Because of limitted number of cases with valvular disease of the heart the results about citrate metabolism are not conclusive.

It should be emphasized that most cases with valvular disease of the heart show congestive heart failure and therefore above described relations among myocardial metabolism, ECG and cardiac size in cases with valvular heart disease represent those in cases with failure. In hypertensive and/or sclerotic cases with failure, similar relationships were observed.

It is concluded that myocardial metabolism has closer relation to cardiac size than to ECG in patients with heart failure and valvular disease of the heart.

2) Hypertension and/or coronary sclerosis.

While the correlation between ST–T and cardiac size was insignificant, QTc and the magnitude of $\hat{G}$ correlated fairly well with cardiac area. The relationship between myocardial metabolism and cardiac area seemed to be poor except a few cases with congestive heart failure. On the other hand, better correlation was obtained between myocardial metabolism and ECG especially ST–T than in cases with valvular disease of the heart. It is therefore supposed that ECG may be influenced directly by myocardial metabolism.

Summary

Correlations of the metabolic state of human heart to ECG and to X-ray findings were studied and discussed.

There was a significant decrease in myocardial citrate extraction and a tendency of disturbed lactate and pyruvate metabolism in the cases with ST–T changes. In many cases with ST–T abnormalities, myocardial oxygen extraction coefficient was increased.

QTc correlated, in general, with oxygen extraction coefficient. The magnitude of $\hat{G}$ in frontal plane showed slight but significant negative correlation with oxygen extraction coefficient.

Oxygen extraction coefficient increased distinctly with the enlargement of the heart in cases with valvular disease, while it was not so apparent in patients with hypertensive and/or sclerotic heart disease without failure.

In cases with cardiac enlargement due to valvular disease of the heart, ST–T abnormalities, increase in QTc and reduction of the magnitude of $\hat{G}$

were frequently observed.

Acknowledgements

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References

1. Weidmann, S.: Elektrophysiologie der Herzmuskelfaser, H. Huber, Bern & Stuttgart, 1956.
2. Brooks, C. McC., *et al.*: Excitability of the Heart, Grune and Stratton, New York and London, 1955.
3. Nachmansohn, D.: Circulation Research **3**: 427, 1955.
4. Trautwein, W., *et al.*: Pflüger's Arch. **263**: 23, 1954.
5. Webb, J. L. and Hollander, P. B.: Circulation Research **4**: 618, 1956.
6. Kardesch, M., *et al.*: Circulation Research **6**: 715, 1958.
7. de Mello, W. C.: Am. J. Physiol. **196**: 377, 1959.
8. Webb, J. L. and Hollander, P. B.: Circulation Research **7**: 131, 1959.
9. Kleinfeld, M., *et al.*: J. Clin. Invest. **34**: 1802, 1955.
10. Lepeschkin, E.: Modern Electrocardiography, Williams and Wilkins, Baltimore, 1951.
11. Barach, A. L. and Steiner, A.: Am. Heart J. **22**: 113, 1941.
12. Taran, L. M. and Szilagyi, N.: Am. J. Med. **5**: 379, 1948.
13. Edson, J. N.: Am. Heart J. **37**: 653, 1949.
14. Roehm, D. C., *et al.*: Am. Heart J. **47**: 204, 1954.
15. White, M. S., *et al.*: Am. Heart J. **24**: 230, 1942.
16. Bing, R. J., *et al.*: Am. J. Med. **15**: 284, 1953.
17. Bing, R. J., *et al.*: Am. J. Med. **15**: 504, 1954.
18. Bing, R. J., *et al.*: Circulation **7**: 71, 1953.
19. Bing, R. J., *et al.*: Circulation **12**: 635, 1955.
20. Kobayashi, T., *et al.*: Jap. Circulation J. **20**: 387, 1956 (In English).
21. Hara, T.: Jap. Circulation J. **20**: 371, 1956 (In English).
22. Kimura, N. and Nakamura, M.: Jap. Circulation J. **20**: 360, 1956 (In English).
23. Goto, Y. and Hosono, K.: Jap. Circulation J. **22**: 501, 1958 (In English).
24. Ito, I.: J. Jap. Soc. Int. Med. **45**: 1020, 1956 (In Japanese).
25. Tsuyuki, H.: J. Jap. Soc. Int. Med. **46**: 265, 1957 (In Japanese).
26. Atsumi, T.: J. Jap. Soc. Int. Med. **46**: 1121, 1957 (In Japanese).
27. Takeuchi, Y.: J. Jap. Soc. Int. Med. **46**: 1153, 1957 (In Japanese).
28. Yasuda, H.: J. Jap. Soc. Int. Med. **46**: 1319, 1958 (In Japanese).
29. Ota, A.: J. Jap. Soc. Int. Med. **46**: 1369, 1958 (In Japanese).
30. Watanabe, M.: J. Jap. Soc. Int. Med. **47**: 1381, 1959 (In Japanese).
31. Hisaoka, A.: Jap. Circulation J. **20**: 87, 1956 (In Japanese).
32. Hisaoka, A.: Jap. Circulation J. **20**: 629, 1957 (In Japanese).

The Influence of the Sympathetic Innervation on Carotid Sinus Activity

Yoshiaki MASUYAMA, M.D.

To investigate the physiological role of the sympathetic innervation of the carotid sinus, an attempt was made to find whether denervation sensitization of the carotid sinus occurs 2 weeks after cutting the sympathetic nerve supply. In cervical-sympathectomized dogs, small amounts of noradrenaline injected directly into the adventitia of the denervated carotid sinus, induced the systemic hypotension and the depression of the carotid occlusion reflexes, while these responses were not found by the same doses of noradrenaline given into the innervated carotid sinus. Thus, evidence of supersensitivity was obtained by the local application of the small amounts of noradrenaline to the denervated carotid sinus area.

THE carotid sinus and aortic buffer reflexes seem to oppose the hypertension by depressing the neurogenic vasoconstrictor outflow. This is the case in acute renal or in chemically induced hypertension in both man and animal. In chronic essential or renal hypertension, as recently shown,[1),2)] the buffer reflex system is, with time, reset to higher pressure levels so that this powerful regulatory system acts to maintain rather than oppose the hypertensive pressure levels. This offers an explanation why hypertension may persist indefinitely after significant quantities of the pressure substances no longer found in the blood. The mechanism by which resetting of the buffer regulatory system occurs is not known. Several factors may be involved. It may depend upon some structural alteration causing a change in elasticity and distensibility of the sinus wall. Kezdi[3)] has shown in dogs that the sympathetic innervation of the carotid sinus can significantly influence baroceptor responses, and this mechanism might play an important role in resetting of the buffer regulatory system.

On the other hand, the degree of pressor response to the vasoactive agents is affected by a great variety of changes. It has been discussed by Page and others[4)–10)] why the blood pressure responses to the vasoactive agents were augmented following the repeated administration of ganglion blockades. Fig. 1 shows an example of this enhanced responses after using tetraethylammonium chloride in anesthetized dog. The responses to noradrenaline (20 gamma) methylisothiourea (30 mg.), wyamine (1.40 mg.) and pitressin (0.3 U.) were shown after 1/25 grain of atropine and 25 mg./Kg. of TEAC. The responses to noradrenaline was further more augmented followeing TEAC than after atropine. A suggestion has been made that this phenomenon would be due

From the Tasaka's Clinic of Internal Medicine, University of Tokyo, School of Medicine, Tokyo.

No. 13. (9/19/58): Normal Dog (♯473-F, ♀, 7.4 Kg.) Anesthetized with Nembutal

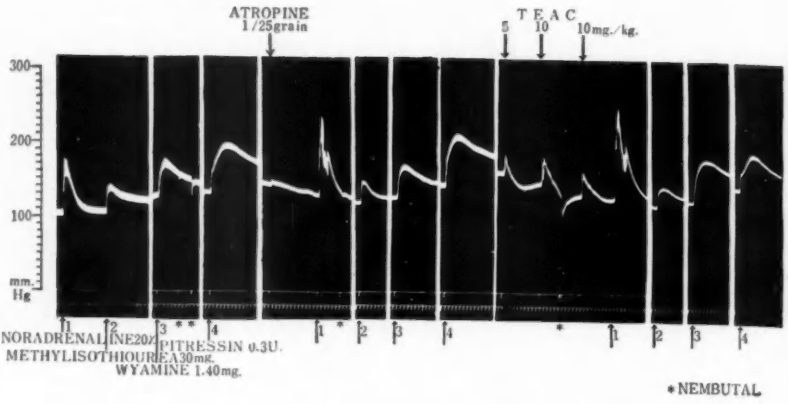


Fig. 1. The responses to 1. noradrenaline (20 gamma), 2. methylisothiourea (30 mg.), 3. wyamine (1.40 mg.) and 4. pitressin (0.3 U.), before and after atropine (1/25 grain) and TEAC (total 25 mg./Kg.). Morphine-pentobarbital anesthesia. Scale at left in mm. Hg. Time marks: 1 minute.

mainly to loss of compensatory cardiovascular reflexes. One of the most important of these, the loss of which enhances arterial responses, is the carotid sinus buffer mechanism. For the discussion of this problem, the influence of the sympathetic innervation on carotid sinus activity must be considered.

About the sympathetic innervation of the carotid sinus, Kezdi[3] has shown that the sympathetic innervation of the carotid sinus might modify the baroceptor activity in dogs. On the other hand, Floyd and Neil[11] found that the stimulation of the sympathetic supply to the carotid sinus had no effect on baroceptors in cats. To investigate this problem, an attempt was carried out to find denervation sensitization of the carotid sinus might occur after cutting the sympathetic nerve supply. If the sensitization occurs, this would offer a supporting evidence for a physiological role of the sympathetic innervtion of the carotid sinus.

Methods

Twelve adult mongrel dogs were anesthetized with morphine (2 mg./Kg.) and pentobarbital (15 mg./Kg.), or pentobarbital alone (30 mg./Kg.) and level of the anesthesia was maintained by intramuscular injection of small doses of pentobarbital. The vagus-sympathetic-depressor trunks were resected, and the top surface of the carotid sinus area was exposed. The arterial pressure was recorded on the smoked drum by a mercury manometer connected to a cannulated femoral artery. Slow infusion of normal saline was given into a femoral vein. Intermittent positive pressure respiration was applied. The experiments were divided into two groups. In the first group (Experiment No. 1–7), 0.05 ml. of 5–25 gamma of noradrenaline

in normal saline solution was injected directly into the adventitia of the carotid sinus area, and the changes in the blood pressure and the carotid occlusion reflexes were observed. In the second group (Experiment No. 8–12), the cervical sympathetic chain was resected low in the neck in one side. About 2 weeks after the sympathectomy, the dogs were used for the experiments, since the supersensitivity of the denervated effectors (denervation-sensitization by Cannon and Rosenblueth[12]) usually would develop at this time. The effects of the denervation were controlled by the Horner's syndrome. The changes in sensitivity to noradrenaline were tested by the injection of 5-25 gamma of noradrenaline directly into the adventitia of the denervated carotid sinus and comparing the resulting fall in arterial pressure and changes of the carotid occlusion reflexes with those following the injection of the same dose of noradrenaline into the adventitia of the innervated side. In some experiments, other vasoactive agents such as angiotensin was used in addition.

Results

Fig. 2 shows one experiment which belongs to the first group. In this case, 30 gamma of noradrenaline was applied subadventitially on the right carotid sinus area. The slight blood pressure fall and the depression of the

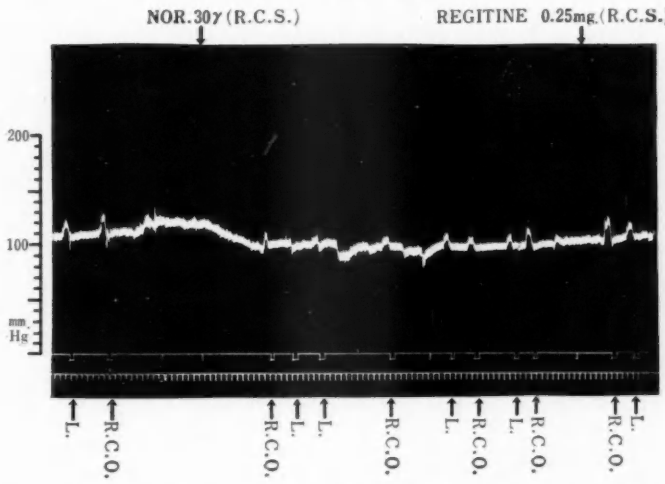


Fig. 2. The responses to noradrenaline (30 gamma) and regitine (0.25 mg.) injected into the adventitia of right carotid sinus area (R.C.S.).

L.: Left carotid occlusion reflexes. R.C.O.: Right carotid occulsion reflexes (injected side). Period of occlusion indicated by signal marker. Time marks: 1 minute.

right carotid occlusion reflexes were observed and 0.25 mg. of Regitine induced the tendency of recovery to the control level. But, this type of the responses was not always clearly shown. In Fig. 3, after the application of 50 gamma

No. 7. (7/29/58): Dog (♯315-F, ♂, 11.7 Kg.)

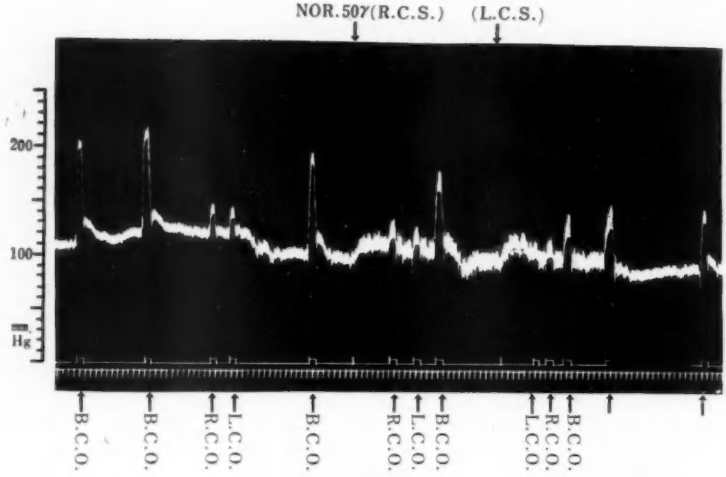


Fig. 3. The responses to noradrenaline (50 gamma) injected directly into the adventitia of right (R.C.S.) and left carotid sinuses (L.C.S.). B.C.O.: Both carotid occlusion reflexes. R.C.O.: Right carotid occlusion reflexes. L.C.O.: Left carotid occlusion reflexes. Time marks: 1 minute.

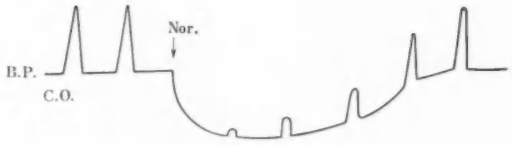
of noradrenaline locally to the right carotid sinus and then to the left carotid sinus, the blood pressure rose in spite of the depressed carotid occlusion reflexes. From this result, it may be assumed that some of the injected noradrenaline might have gone into the blood stream. Table I shows the summarized results of the first experiment group. The mark (+) indicates the typical blood pressure fall and the depression of the carotid sinus reflexes, the mark (−) indicates the negative or the opposite responses, and the mark (±) indicates not-marked responses. Only one half of the experiments showed the typical responses, but with the doses less than 20 gamma, there was no typical responses in this group.

Cervical-sympathectomized dogs 2 weeks after the operation were then used in the second group. Fig. 4 shows the responses after the aplication of 10 gamma of noradrenaline to left and right carotid sinuses in the dog with left cervical-sympathectomy. The blood pressure fall and the depression of the carotid occlusion reflexes were more marked on the denervated side than the innervated side. Fig. 5 shows the same result by using 25 gamma of noradrenaline, and the responses became more marked after the resection of the innervated side of carotid sinuses. Fig. 6 shows the same responses by 5 gamma of noradrenaline on the denervated side before and after resecting the innervated side of carotid sinuses. Fig. 7 also shows those by 5 and 25 gamma of noradrenaline on the denervated side. In Fig. 8, 5 gamma of noradrenaline gave the same results, but 10 units of angiotensin showed no responses

Table I. Results of the First Group—The Responses to Noradrenaline Applied Subadventitially into the Carotid Sinus Area

	Exp. No.	Dose of noradrenaline (γ)			
		20	30	40	50
Blood pressure	1				+
	2	±	+		
	3	±		+	
	4				±
	5				−
	6		−		−
	7				−
Carotid occlusion reflex	1				+
	2	±	+		
	3	±		+	
	4				±
	5				±
	6	+			+
	7				+

Positive Result (+)



either on the blood pressure or carotid occlusion reflexes. Fig. 9 shows the control experiment, using 0.05 ml. of normal saline and 10 units of angiotensin on the denervated side. Both showed no responses on the blood pressure and carotid sinus reflexes, though 5 gamma of noradrenaline showed the typical responses. Table II shows the summarized results of the second experiment group. The marks as +, − and ± indicate the same responses as those in Table I. The mark ( ) indicates the responses when noradrenaline was applied locally on the innervated side, and the mark circle demonstrates those when it was applied on the denervated side after the resection of the innervated carotid sinus. When 5–25 gamma of noradrenaline was applied locally on the denervated side, it induced the typical blood pressure fall and the depression of the carotid sinus reflexes in all the experiments except one in which the responses were not so marked by 5 gamma of noradrenaline. These typical responses were not found by the application of noradrenaline on the innervated side of carotid sinuses. In the control experiment, the same volume of normal saline did not produce any responses. The other vasoactive agent, angiotensin,

No. 10-A. (8/27/58): Dog (♀ 353-F, ♂, 12.8 Kg.) Left Cervival Sympathectomy (8/13/58)

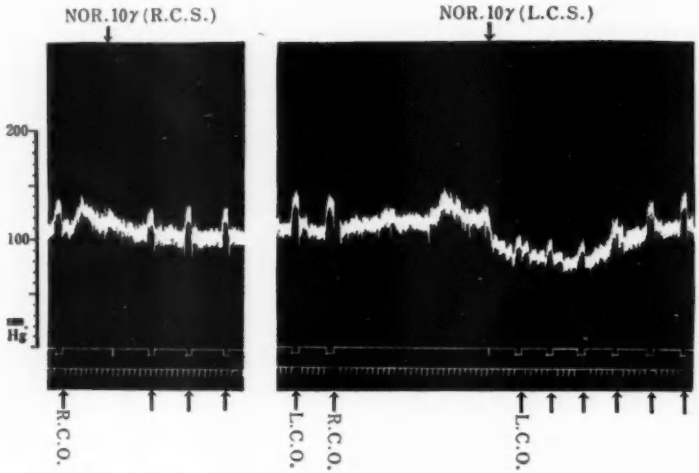


Fig. 4. 2 weeks before the experiment, left cervical sympathectomy was done. The responses to noradrenaline (10 gamma) injected directly into the adventitia of innervated right carotid sinus (R.C.S.) and denervated left carotid sinus (L.C.S.). R.C.O.: Right carotid occlusion reflexes. L.C.O.: Left carotid occlusion reflexes. Time marks: 1 minute.

also failed to show such responses by the local application to the denervated carotid sinus.

Discussion

Heymans[14),15)] has shown that noradrenaline or adrenaline applied locally to the carotid sinus area induced the contraction of this area, and the systemic hypotension and bradycardia occurred reflexly. These circulatory effects have been thought to be induced by the sinusal baroceptor stimulation due to the sinusal contraction. Palme[16),17)] showed the fall of blood pressure by the electrical stimulation of the cervical sympathetic ganglia in animals, and he thought that this occurred through the activity of the sinus. On the other hand, Floyd and Neil[11)] showed that the stimulation of the local sympathetic supply of the carotid sinus did not modify the baroceptor activity of the carotid sinus and did not influence the reflex response of the systemic blood pressure to the changes of perfusion pressure in that sinus, though the stimulation of the sympathetic branches supplying the carotid bifurcation caused an increase in the impulse traffic of the carotid chemoceptor fibers. Kezdi[9)] showed that the continuous electrical stimulation of the isolated sympathetic fibers or superior cervical ganglia, with connection to the carotid sinus only, led to a gradual fall of systemic blood pressure and to decrease in the carotid sinus

No. 9. (8/20/58): Dog (♀316-F, ♂, 12.1 Kg.) Left Cervical Sympathectomy (8/7/58)

Before the Section of R.C.S. After the Section of R.C.S

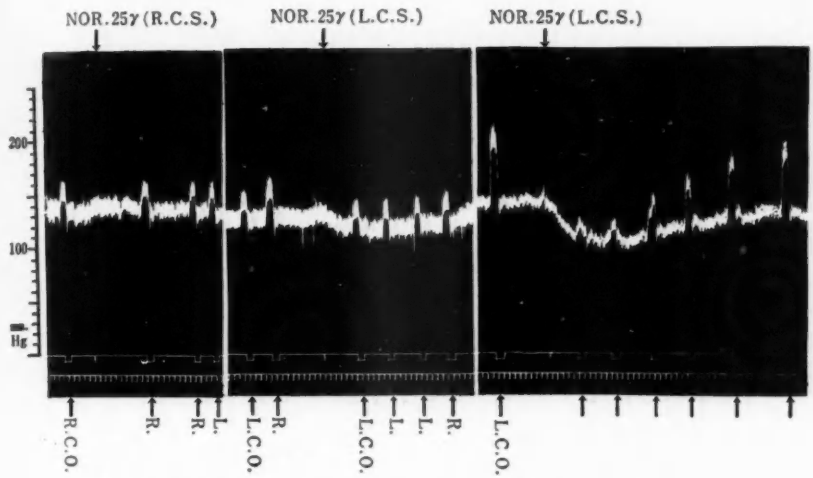


Fig. 5. 2 weeks before the experiment, left cervical sympathectomy was done. The responses to noradrenaline (25 gamma) injected directly into the adventitia of innervated right carotid sinus (R.C.S.) and denervated left carotid sinus (L.C.S.), and those after the section of the innervated carotid sinus (R.C.S.). R.C.O.: Right carotid occlusion reflexes. L.C.O.: Left carotid occlusion reflexes. Time marks: 1 minute.

hypertensive reflex. The effect of the stimulation of efferent sympathetic fibers to the carotid sinus was thought to occur probably by means of noradrenaline release at the nerve endings in the arterial wall and/or adrenaline release from chromaffin cells of the carotid body, which increase the state of contraction of the barosensitive arterial wall, as suggested by Heymans and associates. They suggested that the superior cervical ganglion controlled, at least partially, the state of contraction of the carotid sinus arterial wall and thus had a role in the reflex homeostasis of blood pressure. The disturbance of this innervation could have been a factor in the development of abnormal relaxation and decreased pulsatile expansion of the carotid sinus. Thus it might participate in the pathogenesis of hypertension. The tension and resistance to stretch of the arterial wall, where the carotid sinus pressoreceptors are located, are the fundamental factors affecting these receptors which regulate and moderate reflexly the systemic arterial pressure.[15] Landgren[18] showed the correlation between the impulse activity in the baroceptor fibers and the distensibility of the sinus wall, and it was found that local application of adrenaline to the carotid sinus wall caused an increased distensibility in the region of the physiological blood pressure variation as compared with the control

No. 10-B. (8/27/58): Dog (♯353-F, ♂, 12.8 Kg.) Left Cervical Sympathectomy (8/13/58)

Before the Section of R.C.S. After the Section of R.C.S.

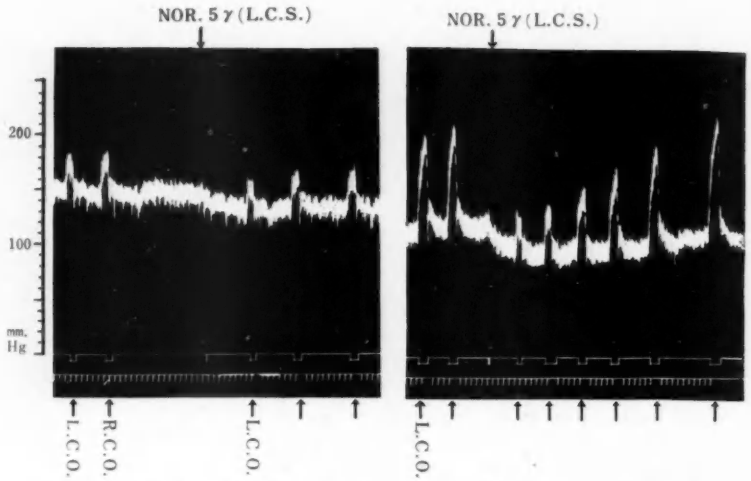


Fig. 6. 2 weeks before the experiment, left cervical sympathectomy was done. The responses to noradrenaline (5 gamma) injected directly into the adventitia of denervated left carotid sinus before and after the section of innervated right carotid sinus. L.C.O.: Left carotid occlusion reflexes. R.C.O.: Right carotid occlusion reflexes. Time marks: 1 minute.

curves. The state of the sympathetic innervation might be considered to influence the distensibility of the carotid sinus area.

Mazzella[19] studied the effects of adrenaline and noradrenaline at different doses injected into the adventitia of the carotid sinus wall and compared with those after the superior sympathetic ganglion extirpation in the chloralosed dogs, and he concluded that the fundamental significance of the sympathetic innervation of the carotid sinus seemed unimportant in normal conditions but it might be more significant in stress of emergency circumstances.

In my experiments the responses to the small amount of noradrenaline injected directly into the adventitia of the carotid sinus area were variable in normal pentobarbital anesthetized dogs and the doses less than 20 gamma of noradrenaline did not show the typical systemic blood pressure fall and the depression of the carotid occlusion reflexes. So, it was not proven that contraction of one sinus induced by physiological doses of the sympathetic hormones can modify the systemic pressure reflexly. But, in the cervical-sympathectomized dogs, even 5 gamma of noradrenaline applied locally on the denervated side induced the typical systemic blood pressure fall and the depression of the carotid sinus reflexes, and the responses to the same amounts of noradrenaline were usually more marked on the denervated side than those on the innervated

No. 8. (8/12/58): Dog (♯329-F, ♀, 12.9 Kg.) Right Cervical Sympathectomy (7/13/58)

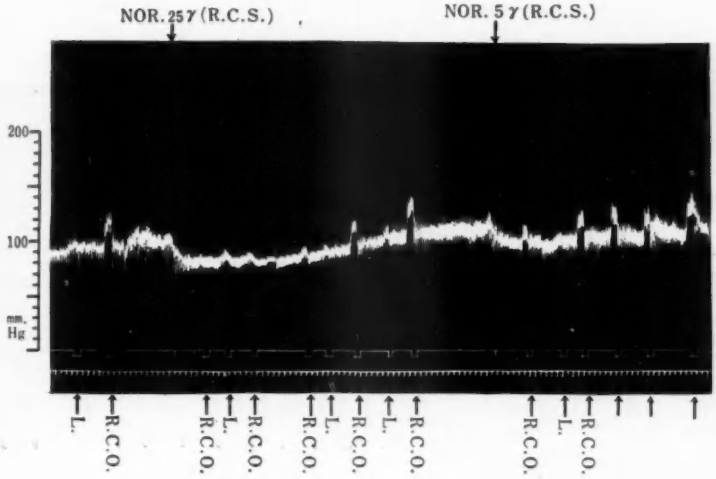


Fig. 7. 12 days before the experiment, right cervical sympathectomy was done. The responses to noradrenaline (5 gamma and 25 gamma) injected directly into the adventitia of denervated right carotid sinus. R.C.O.: Right carotid occlusion reflexes. L.C.O.: Left carotid occlusion reflexes. Time marks: 1 minute.

side, indicating that adrenergic sinusal hypersensitivity produced by sympathetic denervation occurred. Evidence of supersensitivity was obtained by the local application of 5–25 gamma of noradrenaline to the denervated carotid sinus area.

The other vasoactive agent, angiotensin, failed to show the systemic hypotension and the depression of the carotid occlusion reflexes by the local application to the denervated carotid sinus. But it has been shown that normal carotid sinus is quite insensitive to angiotensin.[13]

The mechanism of the augmented responsiveness to the vasoactive agents following the repeated doses of ganglioplegics are not explained only by the depression of the carotid sinus activity, because the increase in the responsiveness that follows the injection of ganglioplegics does not parallel the inhibition of the carotid sinus occlusion reflexes. As another mechanism, a peripheral vascular sensitization allied to that which follows denervation was considered.[10]

Summary

To investigate the physiological role of the sympathetic innervation of the carotid sinus, an attempt was made to find whether denervation sensitization of the carotid sinus would occur 2 weeks after the resection of the sympathetic nerve supply or not. The changes in sensitivity to noradrenaline were examin-

No. 11. (9/4/58): Dog (# 356-F, ♂, 14 Kg.) Right Cervical Sympathectomy (8/15/58)

Before and After the Section of L.C.S.

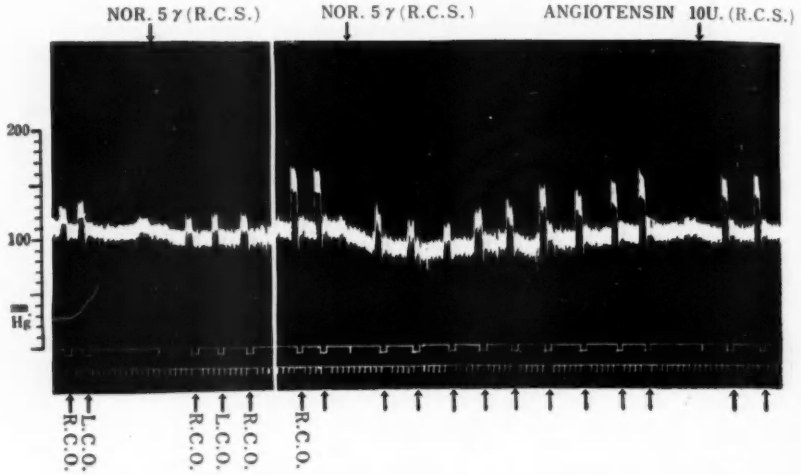


Fig. 8. 20 days before the experiment, right cervical sympathectomy was done. The responses to noradrenaline (5 gamma) and angiotensin (10 units) injected directly into the adventitia of denervated right carotid sinus, before and after the section of innervated right carotid sinus. R.C.O.: Right carotid occlusion reflexes. L.C.O.: Left carotid occlusion reflexes. Time marks: 1 minute.

No. 12. (9/9/58): Dog (# 360-F, ♀, 11.7 Kg.) Left Cervical Sympathectomy (8/21/58)

After the Section of R.C.S.

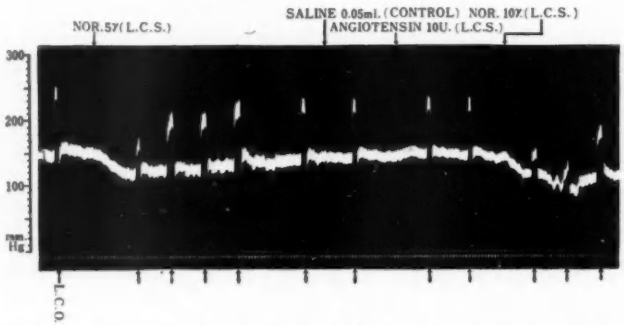


Fig. 9. 19 days before the experiment, left cervical sympathectomy was done. The responses to noradrenaline (5 gamma and 10 gamma), angiotensin (10 units) and 0.05 ml. of saline (as control) injected directly into the adventitia of the denervated right carotid sinus. L.C.O.: Left carotid occlusion reflexes. Time marks: 1 minute.

Table II. Results of the Second Group—The Responses to Noradrenaline Applied Locally into the Carotid Sinus Area on the Denervated Side

Exp. No.	Cervical sympathectomy	Doses of noradrenaline (γ)		
		5 γ	10 γ	25 γ
8	R	+		+ (−)
9	L	±		+ (−)
10	L	+ ⊕	+ (−)	
11	R	+ ⊕		*1
12	L	⊕	⊕	*2

Note: +: B.P. ↓, C.O. ↓
( ): on the innervated side
○: after the section of the innervated carotid sinus
*1 Angiotensin 10 u. −
*2 Saline 0.05 ml., angiotensin 10 u. −

ed by injecting 5–25 gamma of noradrenaline directly into the adventitia of the denervated carotid sinus. The resulting fall in blood pressure and the changes in the carotid occlusion reflexes were compared with those following the injection of the same dose of noradrenaline into the adventitia of the innervated side.

The responses to 5–50 gamma of noradrenaline injected directly into the adventitia of the carotid sinus area were variable in normal pentobarbital anesthetized dogs, and the doses less than 20 gamma of noradrenaline did not show the systemic hypotension and the depression of the carotid sinus reflexes in these dogs.

In the cervical-sympathectomized dogs, 5–25 gamma of noradrenaline applied locally on the denervated side induced the typical blood pressure fall and the depression of the carotid occlusion reflexes in almost all the experiments, while these typical responses were not found by the application of noradrenaline to the innervated carotid sinus.

Angiotensin did not show such responses by the local application to the denervated carotid sinus.

Thus, evidence of supersensitivity was obtained by the local application of 5–25 gamma of noradrenaline to the denervated carotid sinus area. The sympathetic innervation of the carotid sinus seemed to be significant.

Acknowledgements

This investigation is a part of the studies done when the author has been in the Research Division of the Cleveland Clinic Foundation and the Frank E. Bunts Educational Institute. The author would like to express the gratitude to Dr. Page

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References

1. McCubbin, J. W., Green, J. H., and Page, I. H.: Circulation Research **4**: 205, 1956.
2. McCubbin, J. W.: Circulation **17**: 791, 1958.
3. Kezdi, P.: Circulation Research **2**: 367, 1954.
4. Page, I. H.: Am. J. Physiol. **158**: 403, 1949.
5. Page, I. H. and Taylor, R. D.: Circulation **1**: 1233, 1950.
6. Page, I. H. and McCubbin, J. W.: Am. J. Physiol. **168**: 208, 1952.
7. McCubbin, J. W. and Page, I. H.: Am. J. Physiol. **170**: 309, 1952.
8. Collins, D. A.: J. Pharmacol. and Exper. Therap. **94**: 244, 1949.
9. Lum, B. K. B. and Rashleigh, P. L.: Abstracts of Scientific Papers Presented at the Fall Meeting of Am. Soc. Pharmacol. & Exper. Therap. 23: 1958.
10. Page, I. H. and McCubbin, J. W.: Am. J. Physiol. **197**: 217, 1959.
11. Floyd, W. F. and Neil, E.: Arch. Int. Pharmacodyn. **91**: 230, 1952.
12. Cannon, W. B. and Rosenblueth, A.: The Supersensitivity of Denervated Structures, Macmillan, New York, 1949.
13. McCubbin, J. W., Page, I. H., and Bumpus, F. M.: Circulation Research **5**: 458, 1957.
14. Heymans, C. and Neil, E.: Reflexogenic Areas of the Cardiovascular System, Little, Brown & Co., Boston, 1958.
15. Heymans, C., Delaunois, A. L., and van den Heuvel-Heymans, G.: Circulation Research **1**: 3, 1953.
16. Palme, F.: Zeitschrift f. Exper. Med. **113**: 413, 1944.
17. Palme, F.: Exper. Med. & Surgery, **9**: 404, 1951.
18. Landgren, S.: Acta Physiol. Scandinavia **26**: 35, 1952.
19. Mazzella, H. and Mullin, R. G.: Arch. Int. Pharmacodyn. **107**: 54, 1956.

Studies on the Vasomotoricity of the Cerebral Vessels

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On using electropolarography in the rabbit brain in vivo, the spontaneous fluctuations were seen in oxygen availability, having the frequency of 2 components; one of 5 to 15/min., the other of $\frac{1}{2}$ to 1/min. The different areas of brain gave different rhythms, whereas ear-lobes showed on both sides synchronized fluctuations. After extirpation of the superior cervical ganglion, or after an injection of ganglion blocking agent, these fluctuations became synchronous. On the other hand, under nembutal anesthesia or at the time of Biot's respiration, these fluctuations became synchronous with the rate of respiration. It was concluded that these fluctuations may be a representative of cerebral vasomotion having two components: active one of nervous origin and the other passive from general hemodynamics.

FOR many years, it has been demonstrated by many investigators that the cerebrol vessels had anatomical nervous branches, and physiological nervous control. However, it is still not clear in regard to the significance and the magnitude of the nervous control. Moreover, it is still unknown that whether the cerebral vessels, as in peripheral vessels, have rhythmical vasomotion or not, and this has become an interesting problem in recent studies.

Clark and Misrahy,[1] with the method of electropolarography using chronically implanted platinum electrode in cat brain, recorded spontaneous fluctuations, and concluded that "these fluctuations were due to rhythmic variations in blood flow through the finer cerebral vessels". Davies and Bronk,[2] placing a fine electrode on the pial vessels, also reported about "alternate vasoconstriction and vasodilatation".

The purpose of the present study is to analyse the spontaneous fluctuation of electropolarogram (EPG) which we constantly observed in the study of the cerebral microcirculation, comparing with the spontaneous fluctuation observed in the human skin, which has been already reported by Seki,[3] co-author of this paper.

Method and Material

In this study, the electropolarographic recordings were made with electronic arrangement shown in Fig. 1, which is a modification of that described by H.

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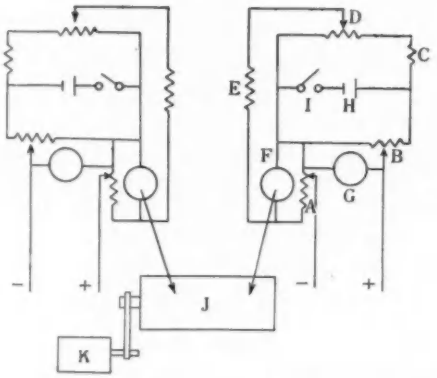


Fig. 1. Circuit diagram of our apparatus of electropolarography.
A: Ayrton's shunt
B: variable resistance (for voltage adjustment) 100 Ω
C: resistance 50 kΩ
D: variable resistance (for 0 point adjustment) 500 kΩ
E: resistance 2 MΩ
F: galvanometer (sensitivity 12×10^{-10} A, period 3.7 sec.)
G: voltmeter
H: dry cell (1.5 V)
I: main switch
J: recording camera
K: motor

Montgomery.[4] With this device, it is possible to record two EPGs from different sites simultaneously on a bromide paper. The galvanometers were Shimazu Co. products, with sensitivity of 12×10^{-10} amp. and frequency of 3.7 seconds. For the cathode, a platinum wire of 0.1 to 0.3 mm. in diameter, insulated to the tip with Cashew insulating paint was used. The exposed tip was less than 1 mm. in length. As the leading wire from the cathode, enameled cupper wire of 0.1 mm. in diameter was used to minimize the disturbing effect occasionally made by restless animals on the recording system. As for the anode, a silver-silver chloride electrode was used and this was made each time before its use. The applied potential was adjusted to 0.6 volt.

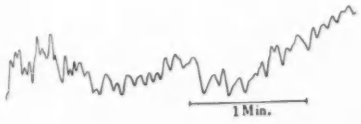
The cathodes were implanted in the brain through each hole in the skull and fixed tightly to the skull with dental cement, whereas the anode was placed subcutaneously.

It is well known that an EPG in vivo represents the tissue oxygen available to the electrode, varying with the local oxygen supply and consumption, i.e. an EPG will be determined by: oxygen concentration in the systemic arterial blood, local blood flow and local oxygen consumption. The oxygen tension of the inspired air being constant, a given EPG will show an index to the local blood flow and local oxygen consumption. In other words, EPG may be said to give an index to the state of local hemodynamics as seen from the side of the tissue.

All experiments here were done on rabbits without anesthesia.

Results

1) When a platinum electrode was inserted and fixed to the skull of a rabbit, the recorded curve always showed spontaneous fluctuation such as shown in Fig. 2. However, the magnitude of the fluctuations were very variable in each case, probably depending on the inserted area of the electrode in the brain as well as the condition of the electrode in the tissue. When two EPGs were recorded simultaneously from two different areas of the brain, both fluctuations were independent in rhythm from each other (Fig. 3).



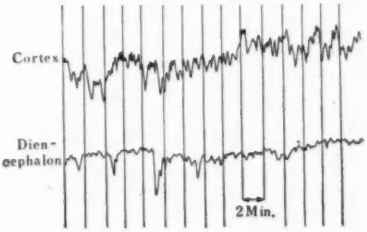


Fig. 2 (Left). A sample of EPG in the rabbit brain (posterior hypothalamus)
Fig. 3 (Right). Comparison of two EPG curves in the rabbit brain.

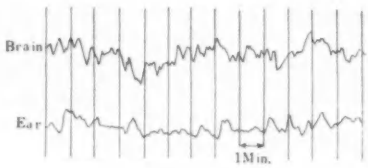
These fluctuations seem to consist of two components: the one wave having a frequency of 5 to 15 cycles per minute, and the other, slower wave of 1/2 to 1 cycle per minute. The rhythms of these fluctuations are easily distinguished from the rhythms of respiration, heart beat and electroencephalogram.

2) When two EPGs were recorded simultaneously, one from the brain and the other from the ear-lobe, each fluctuation was not concordant with the other, irrespective of what region of the brain might be selected (Fig. 4). Meanwhile, two EPGs obtained from the bilateral ear-lobes of the same animal showed a synchronous rhythm, if there was no great temperature difference between the two ear-lobes (Fig. 5). This will prove that the fluctuations in the two ear-lobes are representation of one common phenomenon.

3) When a pricking stimulus was applied to the ear-lobe during the recording of EPGs from the brain and the ear-lobe, a large upward deflection occurred simultaneously in both EPGs (Fig. 6). This peak was followed by a large downward deflection falling below the initial level of the ear-lobe EPG but such phase was scarcely seen in the brain EPG.

4) After the superior cervical ganglion was extirpated on both sides, the fluctuations of the two EPGs, both from the different areas of the brain, now became synchronous. Moreover, in such cases, the fluctuation of brain EPG became nearly synchronous with that of the ear-lobe EPG (Fig. 7).

5) When a ganglionic blocking agent, pendiomide, in does of 25 mg., was injected intravenously, the rhythm of the brain EPG became nearly syn-



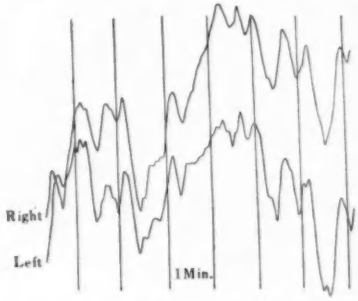
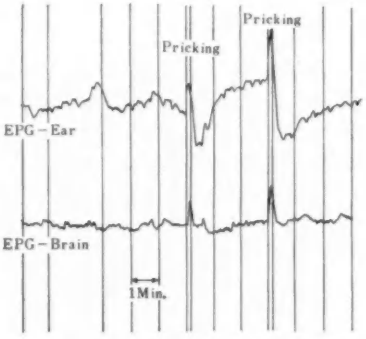


Fig. 4 (Left). Comparison of EPG of the brain with that of the ear-lobe (rabbit).
Fig. 5 (Right). EPGs of bilateral ear-lobes (rabbit).



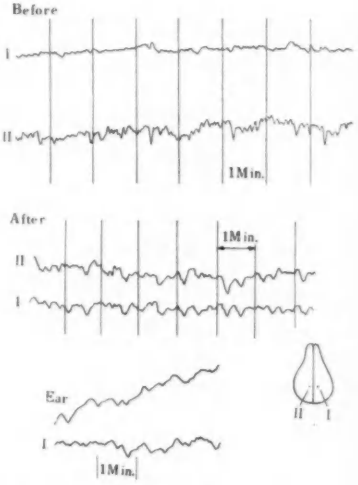


Fig. 6 (Left). Oxygen tension curves (EPG) of the rabbit brain and the ear-lobe influenced by the stimulus of pricking on the ear-lobe.
Fig. 7 (Right). Spontaneous fluctuation of EPGs of the rabbit brain and the ear-lobe before and after the extirpation of superior cervical ganglion.

chronous with that of the ear-lobe EPG (Fig. 8A). Sometimes, there occurred similar changes after the injection of chlorpromazine (Fig. 8B).

6) Upon the nembutal injection, the rhythm of fluctuation in the brain EPG changed markedly in its pattern and became regular and low in amplitude, but sychronous with the slowed respiratory rate, and was followed by a gradual return to the initial rhythm (Fig. 9).

7) At an instance of Biot's respiration, which occurred accidentally fol-

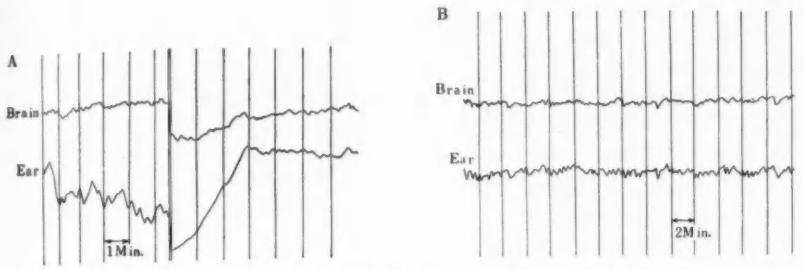


Fig. 8 A (Left). Spontaneous fluctuation of EPGs of the rabbit brain and the ear-lobe before and after injection of pendiomide.

Fig. 8 B (Right). Comparison of EPG of the rabbit brain with that of the ear-lobe after chlorpromazine injection.

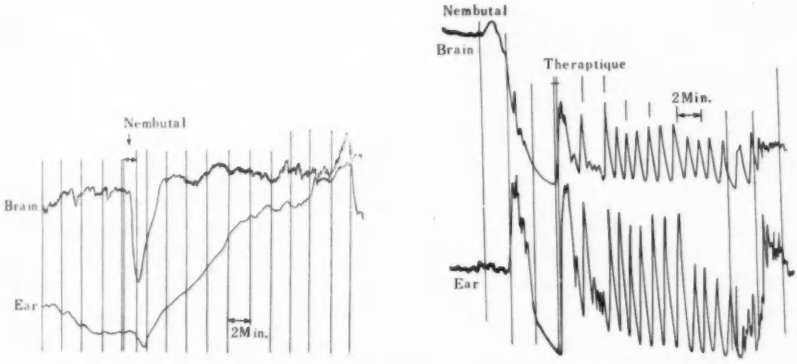


Fig. 9 (Left). Influence of nembutal anesthesia upon the EPGs of the rabbit brain and ear-lobe.

Fig. 10 (Right). Correlation of EPGs of the rabbit brain and ear-lobe when Biot's respiration occurred.

lowing an excessive nembutal anesthesia, the rhythm of both brain and ear-lobe EPGs became synchronous with the respiratory rhythm (Fig. 10).

Discussion

The spontaneous fluctuation of the oxygen tension in the brain was first described in detail by Clark and Misrahy[1] who found spontaneous fluctuations of 6 to 12 cycles per minute on EPG using platinum electrode chronically implanted into the brain of a cat. They observed that the amplitude was reduced by the inhalation of gas containing low oxygen or by the barbital anesthesia, and that the frequency became sinusoidal by the nembutal, and increased by the chloralose anesthesia. Perhaps their reported waves might have

been the same as what we demonstrated in the present study, having nearly the same frequency of fluctuation. The present study supports some parts of the description reported by Clark and Misrahy, but it cannot reconcile with the description that the fluctuation made its appearance after the lapse of several days while in the present study the fluctuation was readily observed soon after an electrode was inserted in the brain. It is our question whether their findings about the effect of nembutal, converting the wave to a sinusoidal pattern, may actually be accounted for a synchronous pattern with the respiration, as shown in the present experiment.

Davies and Bronk[1] applied a fine platinum electrode on the pial artery and vein, and recorded fluctuations of oxygen tension, having the frequency of about 5 cycles per minute. Then, they noted that the waves from artery was eliminated by the inhalation of gas containing low oxygen, but the waves from vein were not affected by such a procedure. From these results, they concluded that these waves might represent the vasomotion, rejecting the possibility of a periodic variation in metabolic rate. Whether their waves are identical with the waves described herein or not cannot be decided because of the different technique employed. Meyer and his associates[5] also recorded similar oscillations on EPG curves from the dog brain, which could be eliminated under hypothermic anesthesia, but they made no speculation about their genetic mechanism.

Seki[3] has employed our method for the studies on the peripheral circulation and found that the skin EPG of extremities in man showed a fluctuation of synchronized rhythm as long as temperature difference between each extremity was small. He came to the conclusion that these findings represented the nervous control of the capillary circulation. On the other hand, Clark and Misrahy have noticed that "electrodes placed 1mm. apart show nearly synchronous patterns, whereas more distantly-placed electrodes show asynchrony".

The present observation illustrated that EPG curves recorded from the brain of rabbit always showed spontaneous fluctuations. These waves could be differentiated into 2 components, a rapid one of 5 to 15 cycles per minute, and a slower of 1/2 to 1 cycles per minute. These fluctuations were analysed first in comparison with the ear-lobe EPG, in which the rhythm was synchronous between the bilateral ear-lobes. This observation seemed to be analogous to Seki's finding in man and suggested that the fluctuation of the ear-lobe EPGs were nervous in origin. However, the rhythm of EPG of the brain was out of phase with that of the ear-lobe EPG, moreover, different areas of the brain gave different waves mutually out of phase, as shown by Clark and Misrahy. In view of these facts, the spontaneous fluctuation in the cerebral oxygen tension seems to be attributed to somewhat other factor than that in the ear-lobe oxygen tension.

Factors responsible for the fluctuation in EPG may be: oxygen supply, oxygen consumption and mechanical factor due to the experimental technique

itself. The last one is most unlikely responsible for the fluctuation in EPG in the present study since possible minor oscillations of the electrode could be eliminated by careful fixation of electrode to the skull. The factor of oxygen consumption, viz. the problem if the brain tissue consumes oxygen rhythmically, may be also put out of consideration, since on ligating the perfusing artery EPG falls smoothly without fluctuation.

Consequently, the problem of the rhythmic oxygen supply to the tissue comes into question. Factors determining the oxygen supply, namely the factors determining the local blood flow are: local vascular resistance, blood pressure and cardiac output. Blood vessels of the brain are known anatomically to be supplied with the sympathetic and some parasympathetic nerves. The extent of such nervous control is generally considered, however, to be much less in the brain than in other parts of the body. The effect of pricking stimulus described in this paper also supports these views, revealing that the brain EPG showed only an upward deflection on stimulus, whereas the ear-lobe EPG showed a similar one but was followed by deep fall, representing a vasoconstriction.

On the other hand, the effect of extirpation of the superior cervical ganglion, making EPGs of the brain synchronous in pattern, and also synchronizing the brain EPG with the ear-lobe EPG, suggests that the fluctuation in the brain EPG is participated by nervous factor. This interpretation is also confirmed by the fact that the rhythm of brain EPG became synchronous with that of ear-lobe EPG after the intravenous injection of pendiomide, a ganglion blocking agent.

When nembutal was injected, the rhythm of brain EPG showed a synchronous pattern with that of slowed rate of respiration, and it was also true in a more exaggerated manner in the case of Biot's respiration. In the latter case, the rhythmic variations in the oxygen saturation of arterial blood and the respiratory fluctuations in the systemic blood pressure are both participant. It is possible that such mechanism may be operative in some extent under the normal conditions.

It can be said, therefore, that the spontaneous fluctuation in the brain oxygen tension depends on both active and passive mechanism. The active one is nervous in origin and it is comparable to, but not identical with, the type of nervous control found in rabbit ear-lobe or in human skin; but the mechanism operative in the brain must be a more complicated one, representing itself in regional variations. The passive mechanism may be hemodynamic in origin and depends on blood pressure, respiration etc. This made its appearance after the nervous mechanism was abolished by such method as the extirpation of the sympathetic ganglion or as the injection of the ganglion blocking agent, also in special forms, under such conditions as the nembutal anesthesia or as Biot's respiration.

Summary

(1) In electropolarogram of the rabbit brain, spontaneous fluctuations were obtained at each time directly after insertion of the platinum electrode; having a frequency of 2 components; a rapid one of 5 to 15 cycles per minute, and a slow one of 1/2 to 1 cycle per minute.

(2) When two EPGs were recorded simultaneously from two different areas of the brain, both fluctuations were independent from each other. The EPGs from brain and ear-lobe also have different rhythms from each other, whereas both ear-lobes showed a synchronous fluctuation.

(3) The factors responsible for these fluctuation were analysed in some detail, and it was revealed that the mechanism was highly complicated one. It was proved that at least two factors were operative; active and passive one. The active one is nervous in origin, so the extirpation of the superior cervical ganglion or ganglion blocking agent had a synchronizing effect on the rhythms of each one of the brain EPGs as well as the rhythm of ear-lobe EPG. The passive factor may be hemodynamic in origin, and this expressed itself in the synchronized waves of brain EPG after the extirpation of the symapthetic ganglion, and also disclosed itself in synchronity with the respiration under the nembutal anesthesia or during Biot's respiration.

(4) It is possible that there still exist other factors related to this problem but still unknown from the present study.

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References

1. Clark, L. C. Jr., Misrahy, G., and Fox, R. P.: J. Appl. Physiol. **13**: 85, 1958.
2. Davies, P. W. and Bronk, D. W.: Fed. Proc. **16**: 689, 1957.
3. Seki, K.: Respiration & Circulation **7**: 1003, 1959.
4. Montgomery, H. and Horwitz, O.: J. Clin. Invest. **27**: 550, 1948.
5. Meyer, J. S. and Hunter, J.: J. Neurosurg. **8**: 601, 1958.

ERRATA

Japanese Heart Journal Vol. 1, No. 2

p. 189, 3rd line
p. 189, 9th line
p. 191, 15th line
p. 197, 6th line

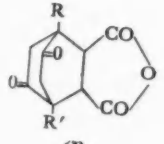
error : -tetrahydroisoindoline
correct : -tetrahydro-4, 7-ethanoisoindoline

Synthesis and Pharmacology of Some Bis-quaternary Salts of the Bicyclo (2.2.2) octane Series, Including 2-(3-Dimethylaminopropyl)-3a, 4, 7, 7a-tetrahydroisoindoline Dimethiodide (KK-25-S)—A New Hypotensive Agent

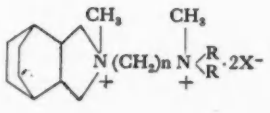
Ken'ichi TAKEDA, Ph. D.,* Keizo KITAHONOKI, Ph. D.,*
Tetsuo MINESHITA, M.D.,* Ryonosuke KIDO, M.D.,*
and Tetsutaro IKEDA, Ph. D.**

2-(3-Dimethylaminopropyl)-3a, 4, 7, 7 a-tetrahydroisoindoline dimethiodide (KK-25-S) is a ganglionic blocking agent for the treatment of hypertension by oral administration. In screening series of bis-quaternary salts containing the bicyclo (2. 2. 2) octane ring for an effective ganglionic blocking agent, the compound KK-25-S was found to excel in activity and duration and to have a low toxicity. From ganglionic blocking activity in cats by intravenous injection it has a potency 3 to 5 times that of Hexamethonium with a 3 to 9 times longer duration. After oral administration KK-25-S is relatively well absorbed, but by comparison of oral activity KK-25-S was inferior to Mecamylamine and Pempidine. However, comparison of the acute toxicity showed this compound to have only half the toxicity of Hexamethonium, the least toxic of all known ganglionic blocking agents. Also, the extremely low parasympathetic blocking activity allows the assumption that clinical side effects will be minimal.

FOR the past several years, the reactions of naphthols,[1),2)] hydroquinone,[3)] and its homologs[4),5)] with maleic anhydride have been investigated in our laboratory; and it was demonstrated that such phenolic compounds can also undergo the usual Diels-Alder reaction, affording directly unique bicyclo-(2. 2. 2) octane derivatives as (I).



(I)



(II)

In connection with this investigation, we now wish to record the synthesis

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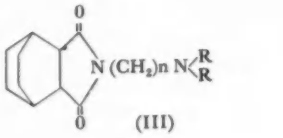
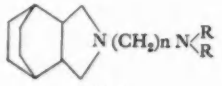
and pharmacology of some bis-quaternary salts containing a bicyclo (2. 2. 2)-octane ring, indicated by the general formula (II). Rice and Grogan[6] have reported on the synthesis of many compounds of a similar type for obtaining active hypotensive agents. However, no bicyclo (2. 2. 2) octane derivatives were found in their studies. We prepared various bis-quaternary compounds mainly by changing the substituents on the octane ring, or the composition of the dialkylamino side chain, for screening on their activity as hypotensive agents.

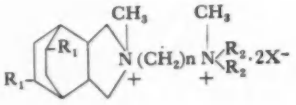
As a starting material we employed the hydroquinone-maleic anhydride adduct (I), as well as the well-known cyclohexa-1, 3-diene adduct. From these adduct anhydrides and the appropriate primary amines, the desired bases were in most cases readily accessible by a two-step process.



(III)

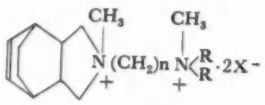


(IV)



V (a-f)

	n	R_1	R_2
Va	2	H	CH_3
b	3	H	CH_3
c	2	OH	CH_3
d	3	OH	CH_3
e	4	OH	C_2H_5
f	3	=O	CH_3



VI (a-i)

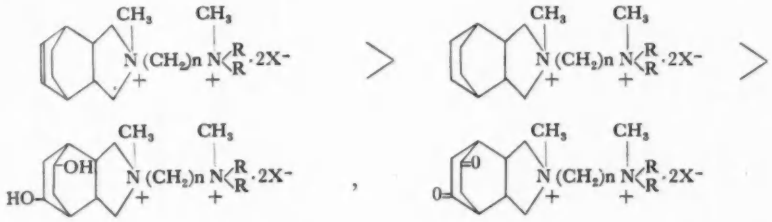
	n	R
VIa	2	CH_3
b	2	C_2H_5
c	2	CH_2·CH=CH_2
d	2	n-C_4H_9
e	3	CH_3
f	4	CH_3
g	4	C_2H_5
h	4	CH_2·CH=CH_2
i	4	n-C_4H_9

The general procedure is as follows: The imide compound (III) was obtained easily by heating the adduct and the primary amine in dioxane, and isolated by vacuum distillation or recrystallization. Reduction of the imide with lithium aluminum hydride gave the corresponding bicyclic base (IV), which was purified by fractional distillation, or recrystallization, or both. When carbonyl groups were present on the octane ring, they were also reduced to the hydroxyl groups, which in some cases could be oxidized back to the carbonyl groups by chromic anhydride in pyridine. The double bond on the

octane ring of the bases can be saturated smoothly by catalytic hydrogenation. By the action of methyl halide in methanol, the imide was converted into the bis-quaternary salt (II), which was obtained in almost all cases in a pure crystalline state.

The bis-quaternary salts thus obtained are shown by the formula (V) and (VI).

In general, the hypotensive activity of the above cited compounds was in the following order.



Furthermore, it was found that when the number of methylens (n) was 2 or 3, the potency was most powerful, while the length of the alkyl groups (R) also played an important role. The order is as follows:

$$CH_3 > C_2H_5 \geqslant CH_2{\cdot}CH{=}CH_2,\ n\text{–}C_4H_9$$

Considering potency, duration of action, side-effects, oral activity, toxicity etc. in animal experiments, 2-(3-dimethylaminopropyl)-3a, 4, 7, 7a-tetrahydroisoindoline dimethiodide (VIe) (KK-25-S) has been found to be the appropriate one of these compounds.

Methods

The various ganglionic blocking agents and KK-25-S were tested intravenously for ganglionic blocking activity. Preganglionic nerve fibers of the superior cervical ganglion and chorda tympani of cats were electrically stimulated, at the frequency of 20 c/s, the duration of 1–2 msec., and the voltage of 1–2 V, for 5 to 10 seconds, in order to test the contraction of nictitating membrane and salivation. The carotid blood pressure was recorded on smoked kymograph paper. In these experiments the cats were anesthetized with methyl-hexabital-Na.

The oral potency of KK-25-S was studied in unanesthetized dogs, making photographic records of relaxing states of nictitating membrane. On the other hand, in order to determine the oral potency of KK-25-S, the pupil responses of the unanesthetized rats were measured after subcutaneous and oral administration.

The effects on isolated toad hearts and rabbit hearts were conducted by the Yagi-Straub's method and Langendorff's method, and the effects on isolated rabbit intestines were observed by Magnus's method.

The following method was employed for charcoal meal test of intestinal transportation. The drug was given orally, and was followed in 20 minutes by oral charcoal meal administration. The mice were sacrificed 30 minutes later, and were

examined for the traversed distance of the charcoal meal.

LD_{50} was determined in mice, rats, and rabbits by intravenous or oral administration.

Results

Action on the Superior Cervical Ganglion of Cats—

The minimal effective dose of KK-25-S was 0.1 mg./Kg. i.v. The inhibitory effects of 0.2 mg./Kg. i.v. were ranged from 40 to 60% with no complete recovery (Fig. 1, Table I).

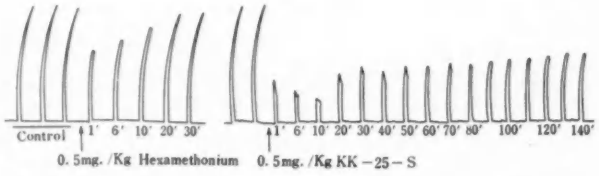
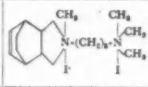
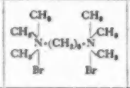
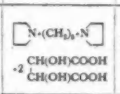
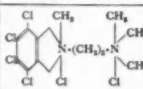


Fig. 1. Comparison of inhibitory action of KK-25-S and Hexamethonium on the contraction of nictitating membrane caused by electric stimulation.

Table I. Comparative Effect of KK-25-S and Other Ganglionic Blocking Agents on the Blood Pressure, Contraction of the Nictitating Membrane and on the Salivation in Cats

Agent	KK-25-S		Hexamethonium		Pentolinium		Chlorisondamine		Pempidine	
Chemical structure										
Hypotensive action (i.v.)	Potency	Duration	Potency	Duration	Potency	Duration	Potency	Duration	Potency	Duration
	5	6~9	1	1	1.5~2	1.5~2	5~5.5	7~11	1	1.5~2
Inhibitory action on the nictitating membrane (i.v.)	3~4	3~4	1	1	2	1.5~2	3~4	4	1	1~1.5
Inhibitory action on salivation (i.v.)	4~5		1	1	2		5		1	

Note: The number of potency and duration was shown as the effective ratio to Hexamethonium, and its value was expressed as 1.

Hypotensive Action in Cats—

The minimal effective dose of KK-25-S for hypotensive activity was 0.025 mg./Kg. i.v.

In many cats, after injection of KK-25-S 0.1 mg./Kg. i.v., blood pressure fell 40 to 50%, and continued for over 3 hours (Table I).

Inhibitory Action on Salivation in Cats—

Intravenous injection of KK-25-S inhibited the salivation which was caused by electric stimulation of the chorda tympani (Table I).

Oral Activity—

Following the oral administration of KK-25-S 2.5 mg./Kg., the nictitating membrane of the dog gradually relaxed. The peak of the relaxation was

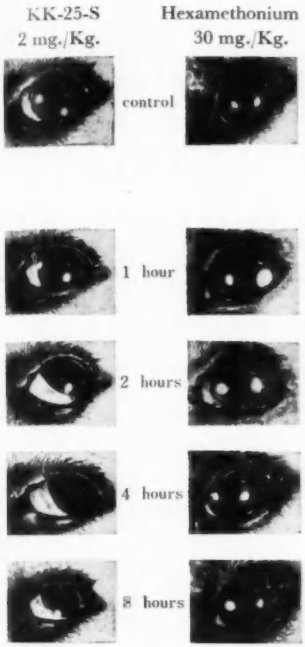


Fig. 2. Comparative effect of orally administered KK-25-S and Hexamethonium on the nictitating membrane in the unanesthetized dog.

Table II. Relaxant Effect of Orally Administered Ganglionic Blocking Agents on the Nictitating Membrane of the Dog

Agent mg./Kg.	Evaluation of the relaxant effect on the nictitating membrane							
	50.0	30.0	10.0	5.0	2.5	2.0	1.0	0.5
KK-25-S				##	##~+	+	±~−	−
Hexamethonium	+	−	−	−				
Pentolinium			+	+	+~±	±~−		
Chlorisondamine					##	##~+	+	−
Pempidine					##	##~+	+	−

Note: ##: Nictitating membrane relaxed more than one-third the size of the eye ball.
+: Nictitating membrane relaxed less than one-third the size of the eye ball.
±: Relaxation of nictitating membrane was slight.
−: Negative.

seen in 4 to 5 hours after the administration (Fig. 2, Table 2).

For the measurement of the oral activity of KK-25-S, mydriatic responses to oral and subcutaneous administration were compared in rats (Fig. 3, Fig. 4).

Effect on Isolated Hearts—

KK-25-S had no effect on the isolated toad heart in a concentration of 10^{-4} (0.1 mg./ml.), also on the isolated rabbit heart by the Langendorff method

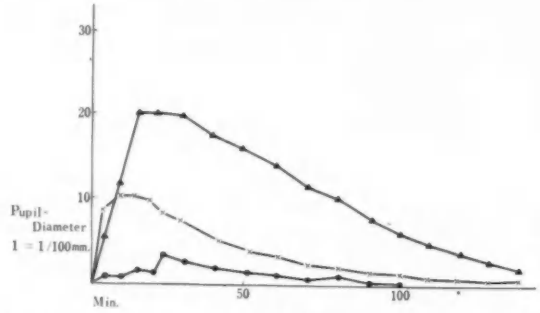


Fig. 3. Effect of the averaged mydriatic responses in a group of 10 un-anesthetized rats. ×, 0.25 mg./100 Gm. KK-25-S ; ▲, 0.25 mg./100 Gm. Chlorisondamine ; ●, 0.25 mg./100 Gm. Pempidine. Drugs were subcutaneously injected.

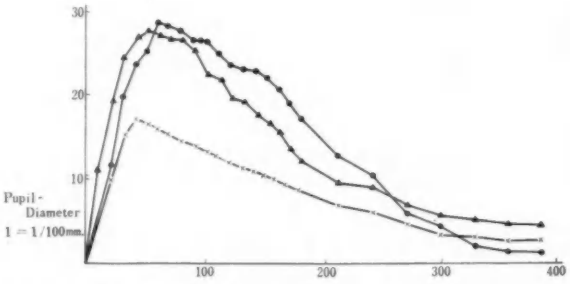


Fig. 4. Effect of the averaged mydriatic responses in a group of 10 un-anesthetized rats. ×, 7.5 mg./Kg. KK-25-S ; ▲, 7.5 mg./Kg. Chlorisondamine ; ●, 7.5 mg./Kg. Pempidine. Drugs were orally administered.

doses up to 5 mg. given directly in the perfusion solution had no effect on either the heart movement or the coronary flow.

Effect on Liver Functions—

In examining the effect of this drug on the liver function of dogs in acute experiments by the galactose tolerance test, 3 daily intravenous injections of 15 mg./Kg. caused its disturbance, but doses of under 5 mg./Kg. showed no effect. On the other hand, by the plasma cholinesterase activity test, 3 daily intravenous injections of 1mg./Kg. caused no disturbance, but doses of 5 mg./Kg. caused a slight disturbance.

Effect on Renal Functions—

As to the effect on renal function in dogs, examination of blood urea concentration by Conway's microdiffusion method showed no tendency to cause azotemia. Also, by inuline and PAH clearance tests, intravenous doses of 0.5 mg./Kg. and 15 mg./Kg. showed no effect on the RPF, but the GFR showed a tendency to increase in the higher dose range.

Effect on Intestine—

This drug had no effect on the extripated rabbit intestine, but by the charcoal meal test in mice, doses over 10 mg./Kg. caused inhibition of passage.

Acute Toxicity—

The intravenous and oral LD_{50} of KK-25-S was determined in different species (Table III).

Table III. Acute Toxicity in Different Species

Agent	Species	Intravenous (LD_{50}) mg./Kg.	Oral (LD_{50}) mg./Kg.
KK-25-S	Mice	156.7	2334.0
	Rats	136.8	1730.14
	Rabbits	82.2	
Hexamethonium	Mice	57.35	1158.6
	Rats	64.13	2890.6
	Rabbits	50.3	
Pentolinium	Mice	44.45	787.0
	Rats	50.76	1568.9
	Rabbits		
Chlorisondamine	Mice	44.47	803.9
	Rats	31.68	300–450*
	Rabbits		

* Presumed value.

Subacute Toxicity—

The toxicity of KK-25-S when administered to rats over a period of 30 days was examined. Six groups of 10 Wister strain male rats with initial body weight of 80 Gm.$\pm$5 Gm., were administered the drug daily according to the following dosage schedule:

subcutaneous	oral
1 mg./Kg.	25 mg./Kg.
5 mg./Kg.	50 mg./Kg.
10 mg./Kg.	100 mg./Kg.

In addition, as control animals one group was subcutaneously injected saline and another group the untreated control group. The growth curves of the groups receiving KK-25-S in doses over 25 mg./Kg. were significantly inferior to those of the control groups.

There were no changes in the erythrocyte and leukocyte counts, hemoglobin or leukocyte analysis of all groups.

The liver weights of the groups receiving over 25 mg./Kg. were significantly increased. Histopathologically, these organs were found to have degenerative changes ranging from cloudy swelling to hydropic degeneration. Mild degenerative changes were also noted in the kidney. However, as these changes are reversible, and taking into consideration the large dosage administered, no great significance was attached to this finding. No other serious changes were observed in any organ either in its weight or its histology.

Chronic Toxicity—

The chronic toxicity of KK-25-S was observed in dogs and monkeys. The animals received 5 mg./Kg. orally for a period of 90 days and during this period examinations for disturbances in liver function and renal clearance were made. In addition, the electrocardiogram was also examined. At the end of the period, the animals were sacrificed, gross findings were recorded and the main organs were prepared for histological examination.

Examination of the liver function by the galactose tolerance test showed no disturbances throughout the 3 month period. Also no marked changes were seen in plasma cholinesterase activity.

In the renal function tests, although no effect was seen in blood urea content, clearance tests indicated that both GFR and RPF showed a tendency to decrease during the initial part of the dosage period. This, however, recovered by the end of the second month.

No changes were seen in the electrocardiograms.

By histological examination, mild degenerative changes, that were classed as cloudy swelling, were noted in the liver and kidney. No marked pathological changes were found in other organs examined..

Discussion

In screening a series of bis-quaternary salts containing the bicyclo(2.2.2)-octane ring for an effective ganglion blocking agent, the compound KK-25-S was found to be potent, long lasting and less toxic.

From ganglion blocking activities in cats, KK-25-S was found to have a potency 3 to 5 times that of Hexamethonium with a 3 to 9 times longer duration.

Comparing various drugs of this type by effect on relaxation of nictitating membrane after oral administration and effective ratio of intravenous to oral administration, the following order was established;

Pempidine > Chlorisadamine ≧ KK-25-S > Pentolinium > Hexamethonium

However, comparison of the acute toxicity showed this compound to have only half the toxicity of Hexamethonium, the least toxic of all known ganglion blocking agents. Also, the extremely low parasympathetic blocking activity allows the assumption that clinical side effects will be minimal.

Summary

(1) A series of some bis-quaternary salts containing the bicyclo (2.2.2)-octane ring has been found to possess hypotensive effect. The relationship between chemical structure and hypotensive effect of these compounds was investigated.

(2) 2-(3-Dimethylaminopropyl)-3a, 4, 7, 7a-tetrahydroisoindoline dimethiodide (KK-25-S) has been found to be the appropriate one as a hypotensive agent of this series.

(3) KK-25-S shows specific ganglionic blocking action with a long duration of action.

(4) After oral administration, KK-25-S is relatively well absorbed.

(5) No evidence of chronic toxicity was observed in dogs and monkeys after the oral administration of 5 mg./Kg. for a period of 90 days.

References

1. Takeda, K., Kitahonoki, K.: Yakugaku Zasshi **73**: 280, 1953 (In Japanese).
2. Takeda, K., Nagakura, S., and Kitahonoki, K.: Pharm. Bull. (Tokyo) **1**: 135, 1953.
3. Takeda, K., Kitahonoki, K., and Igarashi, K.: Pharm. Bull. (Tokyo) **4**: 12, 1956.
4. Takeda, K., Kitahonoki, K.: Ann. **606**: 153, 1957.
5. Kitahonoki, K.: Chem. & Pharm. Bull. (Tokyo) **7**: 114, 1959.
6. Rice, L. M.: J. Org. Chem. **24**: 1520 (1959), and earlier papers cited therein.

Electrocardiographic and Phonocardiographic Studies in Hypertension

Part I. Electrocardiographic Study with Special Reference to the P-Wave

Tsuguya SAKAMOTO, M.D., Goro KAITO, M.D., *and* Hideo UEDA, M.D.*

The P-wave of electrocardiogram in hypertensive patients was studied in comparison with that in normal adults and cases with mitral stenosis. It was suggested that the change in P-wave in hypertension was a reflection of the left atrial overloading possibly resulted from the left ventricular overloading. From the results obtained in this study, we proposed the 7 electrocardiographic criteria, which enabled us to evaluate the left atrial overloading in both cases with hypertension and mitral stenosis.

IT has been noted that the atrial gallop rhythm is one of the characteristic auscultatory findings in hypertensive hearts.[1] The exact mechanism producing this gallop sound is not understood. However, it seems to be due to the overloading of the atrium. Then, such an atrial overloading should be reflected in the P-wave of the electrocardiogram which represent the electrical activity of the atrium. Unfortunately, however, the P-wave in hypertension has not been studied extensively as that in mitral stenosis. In mitral stenosis, a broad notched, sometimes tall, P-wave in the standard leads[2)-9)] or diphasic wave with deep and wide negativity in the right ventricular** leads[10)-12)] are so well known, and they are probably due to the overloading of the left atrium. Therefore, an attempt was made to clarify the P-wave in both conditions of hypertension and mitral stenosis.

Methods and Materials

Three hundreds hypertensive patients including 29 (9.7%) decompensated cases were studied. Their age distribution was varied from 30 to 78 years with an average of 53. Sexual difference was 176 male and 124 female. The majority of these cases were essential hypertension, and their blood pressure was over 160 mm. Hg in systolic and over 90 mm.Hg in diastolic. In 40 patients (13.3%), the diastolic pressure was less than 89 mm.Hg after resting in the supine position for about 20 minutes. The cases with pulmonary emphysema or myocardial infarction were excluded from this series. The follow-up study was made in 12 patients.

One hundred and fifty normal adults were examined as the control group. Their age varied from 30 to 69 years with a mean of 46. This group consisted of

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* Professor of Internal Medicine.

** The term left and/or right ventricular leads used throughout this manuscript indicates the leads in which preponderance of either ventricle appeared in the electrocardiogram.

83 male and 67 female. With careful history and physical examination of these persons, any cases with possible retinopathy and emphysema were excluded. The blood pressure was below 130 mm.Hg in systolic and 80 mm.Hg in diastolic in all cases.

The other control group consisted of 100 cases with pure mitral stenosis. The age ranged from 15 to 60 years with a mean of 32. This group consisted of 29 male and 71 female. The range of blood pressure was 130–110 mm.Hg in systolic and 88–40 mm.Hg in diastolic.

All the cases had normal sinus rhythm, and the cases with disturbances of the rhythm were excluded.

Routine 12 leads of the electrocardiogram were taken in all cases with usual photographic recording device. The paper speed was 40 to 50 mm. per sec. (in some cases 80 to 120 mm.), and the calibration was customary 1 mV. per 10 mm. for standard leads and 5 mm. for precordial leads (in some cases 10–15 mm. for both standard and precordial leads are used).

The electrocardiographic study was made mainly on the P-wave, and its duration, amplitude, electrical axis, and their morphology were analysed.

For the evaluation of the P-wave duration and PR-interval, the maximal values of three standard leads were used, and the index of Macruz[13] was calculated by these measurements. By using 5 ×magnifying-glass, the amplitudes of the P-wave were measured up to 0.1 mm.in the leads I, II and left ventricular leads. The peak interval was used for the measurement when there was notched P-wave present. The mean atrial and ventricular vector (ÂP and ÂQRS) was calculated from the areas in the three standard leads.[14] Morphology in V_1 was classified on the basis of predominancy of positive or negative areas that signify the right or left atrial preponderance.[15]

T-test was performed and the p values were obtained in order to establish the statistical significance.

Results

1) *Duration of the P-wave*:

Comparing to the normal, a significant prolongation of the duration of the P-wave was seen in hypertensive group including mild case ($p<0.01$) (Table I and Fig. 1). This prolongation appeared to have good correlation with diastolic blood pressure level. In other words, the higher the diastolic pressure is, the longer the duration of the P-wave. There was no distinctive difference of the duration of the P-wave between hypertensive and mitral stenosis ($p>0.05$) (Table I). The average duration of the P-wave in normal was less than 0.10 sec. and rarely it exceeded the value of 0.11 sec. (Fig. 1).

2) *PR-interval*:

There was no significant difference in PR-interval noted among normal, hypertensive and mitral stenosis ($p>0.05$) though there was some tendency of its prolongation in the cases with severe hypertension ($p<0.05$) (Table I).

3) *Index of Macruz*:

In hypertensive group, according to the elevation of their diastolic pressure

Table I. P-wave Duration, PR-interval and Index of Macruz

		No. of cases	Duration (sec.)		PR-interval (sec.)		Index of Macruz		
			Range	Mean	Range	Mean	Range	≧1.6 ( )=%	≦1.0 ( )=%
Normal adults		150	.06～.12	.092 ±.011	.12～.20	.157 ±.010	.8～3.0	Cases 51 (34.0)	15 (10.0)
Mitral stenosis		100	.08～.14	.108 ±.013	.12～.20	.157 ±.019	.7～7.0	82 (82.0)	2 (2.0)
Hypertension Diastolic blood pressure level	mm. Hg ～89	40	.08～.13	.097 ±.013	.12～.20	.162 ±.021	.8～3.3	19 (47.5)	5 (12.5)
	90～99	68	.07～.13	.098 ±.012	.12～.20	.161 ±.018	1.0～3.3	28 (41.2)	4 (5.9)
	100～109	68	.08～.13	.106 ±.011	.13～.20	.167 ±.021	1.0～3.7	39 (57.3)	1 (1.5)
	110～119	65	.08～.15	.109 ±.013	.12～.20	.164 ±.021	1.1～4.3	51 (78.5)	0 (0.0)
	120～129	34	.08～.14	.111 ±.015	.13～.20	.162 ±.022	1.1～5.5	28 (82.4)	0 (0.0)
	130～	25	.09～.14	.111 ±.013	.13～.20	.171 ±.023	1.2～5.5	22 (88.0)	0 (0.0)
	Total	300	.07～.15	.105 ±.014	.12～.20	.164 ±.020	.8～5.5	182 (62.3)	10 (3.3)

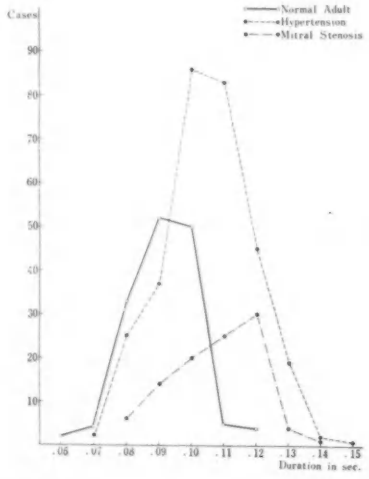

Fig. 1. Duration of the P-wave in a total of 550 cases. In a majority of normal subjects, the maximal duration of the P-wave does not exceed 0.10 sec. While, in many cases with mitral stenosis, it is 0.11 sec. or greater. In hypertensives, it is also greater than 0.11 sec. in a half of cases.

level, the evidence of the frequent incidence of left atrial overloading was noted (Table I). However, equivocal sign of the left atrial overloading was also noted in 34% of normal.

4) *Amplitudes of the P-wave*:

This is also correlated with the level of the diastolic pressure, and it was the highest in mitral stenosis (Table II). There was only a few cases with normal heart in which the amplitude of the P-wave exceeded 0.11 mV. in lead I and 0.16 mV. in lead II. Therefore, a significant increase in amplitude of the P-wave was seen in hypertensive group comparing with the normal ($p<0.01$).

Table II. Amplitudes of the P-wave (unit=0.1 mV.)

		No. of cases	I		II		V_5		V_6	
			Range	Mean	Range	Mean	Range	Mean	Range	Mean
Normal adults		155	.0~1.6	.68 ±.27	.5~2.0	1.07 ±.30	.1~1.3	.50 ±.28	.0~1.2	.42 ±.19
Mitral stenosis		100	.6~3.0	1.31 ±.41	.3~3.9	1.96 ±.77	.3~2.6	1.24 ±.48	.4~3.3	1.27 ±.55
Hypertension Diastolic blood pressure level	mm. Hg ~ 89	40	.1~2.0	.87 ±.34	.2~1.8	1.00 ±.37	.2~1.3	.71 ±.26	.1~1.0	.53 ±.22
	90~ 99	68	.2~1.4	.83 ±.21	.3~2.2	1.15 ±.39	.2~1.5	.65 ±.29	.0~1.2	.53 ±.28
	100~109	68	.3~1.8	.94 ±.37	.3~2.0	1.19 ±.37	.1~1.7	.74 ±.30	.0~1.4	.58 ±.28
	110~119	65	.2~2.0	.97 ±.37	.0~2.4	1.28 ±.51	.2~1.6	.80 ±.29	.1~1.4	.71 ±.29
	120~129	34	.3~2.0	1.02 ±.37	.5~2.4	1.36 ±.53	.3~2.0	.87 ±.34	.3~1.3	.75 ±.25
	130~	25	.3~1.8	1.13 ±.36	.3~2.6	1.51 ±.62	.4~1.5	1.04 ±.38	.3~1.8	.98 ±.40
	Total	300	.1~2.0	.94 ±.32	.0~2.6	1.22 ±.46	.1~2.0	.76 ±.32	.0~1.8	.64 ±.31

The P-wave in left ventricular leads increased in their amplitude according to the severity of hypertension. The result is summarized in Table II. There was a significant increase in the amplitude of the P-wave in hypertensive group comparing with the normal ($p<0.01$).

5) *Morphology of the P-wave in the standard and left ventricular leads*:

Notched P-wave in standard leads was seen in 88% of mitral stenosis, 63% of hypertension and 27.3% of normal. The time interval between the first and the last peak of the P-wave varied in 3 groups. The mean of this peak interval was 0.033 sec. in normal, 0.043 sec. in hypertension and 0.048 sec. in mitral stenosis. However, in severe hypertension and severe mitral stenosis, this interval in lead I and II was difficult to be determined because it has frequently three- or multi-peaked configuration in its shape (Fig. 2). Consequently the significance of this interval in different diseases is doubtful.

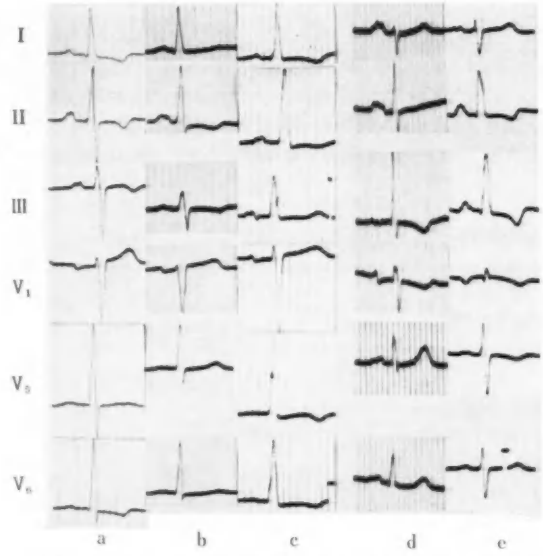

Fig. 2. Electrocardiograms demonstrating the changes of the P-wave in three standard leads and right or left ventricular leads (a, b and c: hypertensive cases; d and e: cases with mitral stenosis). The calibration is 1 mV. per 10 mm. for the standard leads in all cases and for the precordial leads in the case d. It is 1 mV. per 5 mm. for the other precordial leads. Full descriptions for the findings of these P-wave changes are in text.

In contrast to the standard leads, definite classification of the morphology was always possible in the left ventricular leads. The smooth convexity type of the P-wave was predominating finding in normal, and bifid in most of the hypertensive and mitral stenosis (Table III). The same interval between 2 notches of the P-wave was 0.036 sec. in normal and 0.044 sec. and 0.051 sec. in hypertensive and mitral stenosis, respectively. The p value between the normal and abnormal cases was less than one in one hundred, and indicates a significant finding. There was only slight correlation between the peak interval and the duration of the P-wave. In general, there was a preponderance of the second peak of the P-wave in the left ventricular leads, however there occurred a reverse type, namely the preponderance of the first peak in some cases of severe mitral stenosis. There were also some cases with blurred P-waves in left ventricular leads, and they were included in this series when a definite bifid P-wave with peak interval of 0.04 sec. or more was seen in the standard leads. The difference in the incidence of this bifid P-wave between normal and abnormal cases, was significant ($P<0.01$) (Table III).

6) *The mean vector of the P-wave*:

There was more marked left axis deviation of the P-wave in hypertension than in normal (Table IV). In normal, the mean axis of the P-wave was

Table III. Incidence of Various P-wave Morphology in the Left Ventricular Leads (V_5, V_6) ( )=%

	Type→		Convex	Impure 1st peak	Impure 2nd peak	1st peak		Equal peaks		2nd peak		Bifid wave —Total—	Bifid wave Peak interval 0.04"~
						—Total—	Peak interval 0.04"~	—Total—	Peak interval 0.04"~	—Total—	Peak interval 0.04"~		
Normal adults		Cases 150	110 (73)	4 (3)	21 (14)	1 (1)	0 (0)	8 (5)	5 (3)	6 (4)	4 (3)	15 (10)	9 (6)
Mitral stenosis		100	5 (5)	0 (0)	30 (30)	7 (7)	7 (7)	3 (3)	3 (3)	55 (55)	54 (54)	65 (65)	64 (64)
Hypertension Diastolic blood pressure level	mm. Hg ~ 89	40	(65)	(5)	(15)	(3)	(3)	(5)	(3)	(8)	(8)	(15)	(13)
	90~ 99	68	(51)	(6)	(16)	(6)	(4)	(7)	(6)	(13)	(10)	(27)	(21)
	100~109	68	(29)	(6)	(34)	(4)	(1)	(10)	(10)	(16)	(16)	(31)	(28)
	110~119	65	(14)	(0)	(29)	(3)	(3)	(17)	(15)	(37)	(35)	(57)	(54)
	120~129	34	(9)	(0)	(23)	(3)	(3)	(24)	(21)	(41)	(41)	(68)	(65)
	130~	25	(3)	(0)	(16)	(0)	(0)	(20)	(20)	(60)	(60)	(80)	(80)
	Total	300	94 (31)	10 (3)	71 (24)	11 (4)	8 (3)	38 (13)	34 (11)	76 (25)	73 (24)	125 (42)	115 (38)

paralleled to that of the QRS with the angle of ± 30, but there occurred insignificant change in the mean of the P-wave in spite of the marked left axis deviation of the QRS (Fig. 3). On the other hand, in 79% of mitral stenosis, there was a tendency of left axis deviation more than 30 degrees in the mean of the P-wave than that of QRS (Fig. 3). An "absolute" or a "relative" left axis deviation* of the P-wave is frequently seen in mild hypertension and mitral stenosis. In severe hypertension with congestive heart failure, a marked left axis deviation of the QRS was seen, yet the mean of the P-wave had a tendency of right axis deviation (Table IV). In these instances, there occurred tall, broad and multi-peaked P-wave frequently (Fig. 2).

7) *Morphology of the P-wave in the right ventricular lead*:

* The term "absolute" and/or "relative" left axis deviation of the P-wave used in this report is in a sense that the mean vector of the P-wave is less than +30 degrees (absolute), and is greater than 30 degrees in the difference between the mean vector of QRS and P ($\bar{A}QRST—\bar{A}P \geqq 30$ degrees: relative left axis deviation).

Table IV. ÂP and ÂQRS (unit=degrees)

			ÂP		ÂQRS	
			Range	Mean	Range	Mean
Normal adults		150	+90∼− 5	+57±19	+100∼−40	+53±31
Mitral stenosis		100	+80∼−30	+39±27	+150∼−10	+86±24
Hypertension* Diastolic blood pressure level	mm. Hg ∼ 89	40	+90∼−30	+41±27	+100∼−40	+33±38
	90∼ 99	68	+80∼−10	+47±19	+ 95∼−50	+36±33
	100∼109	68	+80∼−30	+43±22	+100∼−30	+36±26
	110∼119	65	+80∼−30	+45±22	+100∼−50	+29±36
	120∼129	34	+80∼−30	+44±26	+ 70∼−30	+29±31
	130∼	25	+85∼± 0	+49±21	+ 70∼−30	+26±25
	Total	300	+90∼−30	+45±23	+100∼−50	+33±32
*Decompensated cases		29	+85∼−10	+49±23	+ 70∼−50	+26±32

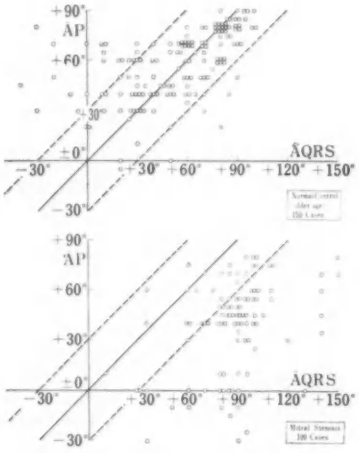

Fig. 3. The mean axes of P and QRS in normal adults (above) and the cases with mitral stenosis (below). The relationship of ÂP to ÂQRS is quite different in each condition. Details in text.

As shown in Table V, the present study disclosed the preponderance of the negative area in lead V_1 in the cases with hypertension and mitral stenosis, namely in these instances, the vectorial orientation of the P-wave in the horizontal plane pointed backward in many cases.

8) *Comparison of the amplitude of the P-wave in the leads V_5 and V_6:*

In the cases with no bifid P-wave in the left ventricular leads, there was no instance that the amplitude of the P-wave in lead V_6 was more prominent

Table V. Morphology in Lead V_1 ( )=%

		No. of cases	Positive	Diphasic			Negative	Predominant negative —Total—
				Greater positivity	Equally positive & negative area	Wide & deep negativity		
Normal adults		150	64 (43)	42 (28)	21 (14)	22 (15)	1 (1)	23 (16)
Mitral stenosis		100	3 (3)	9 (9)	8 (8)	62 (62)	18 (18)	80 (80)
Hypertension Diastolic blood pressure level	mm. Hg ~ 89	40	11 (28)	14 (35)	2 (5)	11 (28)	2 (5)	13 (33)
	90~ 99	68	12 (18)	24 (35)	5 (7)	25 (37)	2 (3)	27 (40)
	100~109	68	9 (13)	17 (25)	7 (10)	31 (46)	4 (6)	35 (51)
	110~119	65	4 (6)	10 (15)	6 (9)	40 (62)	5 (8)	45 (71)
	120~129	34	3 (9)	3 (9)	2 (6)	23 (68)	3 (9)	26 (76)
	130~	25	1 (4)	3 (12)	2 (8)	16 (64)	3 (12)	19 (76)
	Total	300	40 (13)	71 (24)	24 (8)	146 (49)	19 (6)	165 (55)

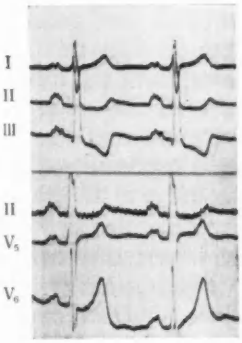

Fig. 4. The standard and the left ventricular leads in a case with mitral stenosis (simultaneous recording). P_I has a typical bifid shape with its peak interval of 0.05 sec. While, the morphology in leads II and III are the multiple-peaks type. Note the finding that the amplitude of the P-wave in lead V_6 is much greater than that in lead V_5 in its second peak.

than in V_5. On the contrary, in the cases with severe hypertension and in the cases with mitral stenosis, there occurred frequently the bifid P-wave in which the second peak was taller in V_6 than that in V_5 (Figs. 2 c, e and 4). This finding had no correlation with either the height of R-wave in the left ventricular leads or the differences of the axis deviation of the P-wave in the standard and the right ventricular leads. These results obtained in the study will be postulated and discussed later.

Discussion

Since the original description by Lewis[2] in 1913, an abnormal P-wave in electrocardiogram associated with mitral stenosis has been studied by many

investigators. However, the frequency of the appearance of this P-wave in mitral stenosis differs from one author to another. Moreover, it is occasionally seen partly even in normal individual without any history of rheumatic heart disease. In addition, as stated at the beginning of this paper, the similarity of the P-wave between hypertension and mitral stenosis seems to offer an explanation that the P-wave change in hypertension might have been due to the overloading of the left atrium. Because of this point of view, a massive comparative study was undertaken to clarify the P-wave changes in above-mentioned conditions.

From the results obtained in the present study, some assumptions may be postulated. As far as the duration of the P-wave is concerned, no new evidence or aid for the diagnosis of abnormality of the P-wave was found. The average duration of this P-wave in normal is less than 0.10 sec. as in the previous studies by others.[14),16),17)] On the other hand, the prolongation of the P-wave was often found in mitral stenosis and hypertension even in the mild cases. This finding is also in accordance with Sodi-Pallares.[18)] However, one needs to call attention to the fact that the normal duration of the P-wave is not necessarily exclusive of the abnormal state of the left atrium. It is also true to almost all the above-mentioned findings of the P-wave.

As to the PR-interval, there was no significant difference between normal and abnormal group. Since the index of Macruz is mathematically driven from the duration of the PR-interval vs. PR-segment, it will not be significant index when the former is constant, because the incidence of an abnormal value in this index depends only upon the duration of the P-wave. Moreover, we found many cases of normal persons belonged to the range of the left atrial overloading (Table I). For these two reasons, we could not adopt this index as the criterion for evaluating the atrial overloading in this study.

According to White,[17)] the increased amplitude of the P-wave was noted in the hypertensive cases associated with myocardial insufficiency, and our data in hypertension were essentially identical to his opinion. The mean value of the amplitude of the P-wave in our normal subjects was 0.68 and 1.07 mm. in leads I and II, respectively (Table I). These figures are exactly the same to that obtained by Kossmann.[19)] The reason for the selection of the lead I and II for the purpose of comparison was based on the facts that, in mitral stenosis, there were two types of prominent P-wave in either leads I and II or II and III, and in the former, the P-wave in lead III was diphasic or negative, so that unmeasurable with a certain accuracy. Some cases of clinically severe mitral stenosis and hypertension in our study revealed the prominent P-wave in both leads II and III, which appeared to be reflected from the overloading of the right atrium as described by White and Burwell[20)] and other authors. However, the overloading of the right atrium in both cases with mitral stenosis and hypertension is always secondary to that of the left atrium unless there is some evidence of pulmonary emphysema, the possibility of which was excluded in our study. Therefore, it will be justifiable to assume

that the mitral and hypertensive cases accompanying the prominent P-wave in lead II and III are more advanced cases than those with the prominent P-wave in lead I and II, because both left and right atrial overloading are most likely present in the former condition (biatrial overloading). Such P-wave caused by biatrial overloading, which named " P-cardiale " by Schmidt,[21] is quite different from the " P-pulmonale " in its duration and shape. The former usually manifests itself as a wide and multi-notched P-wave and the latter as a narrow, tall and non-notched one. Such a tall multi-notched P-wave with widening in duration seen in the cases with mitral stenosis and severe hypertension has been termed as " prefibrillatory "[22] or " sclerotic " P-wave by some authors.

As it is evident from the above-mentioned description, there occurs a tendency to the right axis deviation of the P-wave in severe mitral stenosis, although the left axis deviation of the P-wave is one of the most characteristic findings in the cases with mitral stenosis. However, it is interesting to observe the fact that the right axis deviation of the P-wave is by far less grade compared with that of the QRS complex in the cases with mitral stenosis (Fig. 3). This suggests that, compared with the figure in normal, the P-wave in that instance has a tendency to left axis deviation in spite of the marked right axis deviation of the ventricular complex (" relative " left axis deviation of the P-wave). Although this figure is seen in normal in slight degree (Fig. 3), it is more characteristic to mitral stenosis and also mild hypertension. The nature of this figure is probably due to the concomitant overloading in the different side of the heart, as seen in mitral stenosis, namely, in this occasion, the overloading of the right ventricle and that of the left atrium is present. However, this finding is also evident in hypertension where the same side of the heart is overloaded. On the contrary, the left axis deviation of the P-wave may disappear in severe hypertension in spite of the marked left axis deviation of the QRS. This is probably due to the biatrial overloading secondary to that of the left atrium. In this instance, however, the marked change in the P-wave are noted in its duration, height and shape, and these changes are sufficient to exclude the evidence of milder degree of the left atrial overloading and to recognize the one of the severe degree of its overloading. It is evident, therefore, the left axis deviation of the P-wave is regarded as one of the earliest electrocardiographic signs of hypertension, as stated by Sodi-Pallares.[18] And this change in the axis of the P-wave is not so attributable to the secondary phenomenon due to the left axis deviation of the QRS as noted by Schmidt[21] and others.[23]

Similar pathognomonic finding of the P-wave is also observed in lead V_1. In this lead, diphasic shape with widened and deepened negative portion of the P-wave is noted even in early cases of both hypertensive and mitral stenosis. Cabrera and Sodi-Pallares[24] also observed similar finding in hypertension and stated that this increased negativity of the P-wave in lead V_1 would be the only sign in the early stage of hypertension, and would indicate some evidences

of the left atrial overloading. Our result supported their observation as well.

In both hypertensive and mitral stenosis, the left ventricular leads show abnormal P-wave. The P-wave in severe hypertension has a definite notch with increased interval between the peaks just as in mitral stenosis. The same finding in mitral stenosis has been confirmed by Thomas and Dejong using CR leads.[25] This provides us with the diagnosis and the classification of the severity in both hypertensive and mitral stenosis. In addition, the slurred impure second peak type of the P-wave in the left ventricular leads, was seen in the mild cases with mitral stenosis. It seemed to us that this shape did not differ essentially from the bifid wave, when that was accompanied by the definite notch in the standard leads. Therefore, this figure would be also helpful in the diagnosis of the severity in both hypertensive and mitral stenosis.

Although the amplitude of the P-wave in the left ventricular leads has not been so much evaluated as that in the standard leads, the increased amplitude in the former would be a good reflection of the increased overloading of the left atrium. Though the amplitude of the P-wave in left ventricular leads in the aged generally has a tendency to decrease in its height,[26] the value in severe hypertension obtained in our study increase significantly in spite of their older age.

The finding that the amplitude of the P-wave in lead V_6 is taller than that in V_5 would be the most reliable sign of the left atrial overloading, because this figure is seen in the second peak of the P-wave in these leads in the cases with severe hypertension and mitral stenosis. Although we could not obtain any correlations between this figure and the other findings of the electrocardiogram, it should have some relation to the definite left and posterior deviation of the P-vector, which was displayed in mitral stenosis by Sano and his associates[27] and others.[15]

Criteria to assess the change of the P-wave in both hypertensive and mitral stenosis: From the results obtained and the above-mentioned discussion, we will propose the 7 electrocardiographic criteria (Table VI), which enable us to evaluate the left atrial overloading in both conditions. The incidence of each criterion was listed in Table VII. There was a significant difference in the incidence of each criterion between normal and mitral stenosis ($p<0.001$) as well as hypertension ($p<0.001$). As to all criteria, hypertensive fell midway between the other two groups. Moreover, the incidence of many criteria in severe hypertension was equal to that in mitral stenosis. Unfortunately, however, we could not avoid some overlapping of the incidence of each criterion, exclusive of G, between normal and abnormal conditions. For example, the amplitude in the standard leads over 3.0 mm., which was determined as upper normal limits by some author,[14] was rarely seen in even mitral stenosis, and similar observations were also true in almost all criteria. This does not enable us to distinguish the abnormal conditions from the normal one, when we use only one or two pathological findings, namely the one represented in only either frontal or horizontal pro-

Table VI. Criteria to Assess the Changes in the P-wave

A) Duration: 0.11 sec. or more in standard leads
B) Amplitude: $P_I = 0.11$ mV. or more; or $P_{II} = 0.16$ mV. or more
C) Electrical axis ($\hat{A}P$): $\hat{A}P \leqq +30°$; or $\hat{A}QRS - \hat{A}P \geqq 30°$
D) Morphology in V_1: diphasic (deep and wide negativity) or negative
E) Morphology in standard leads and left ventricular leads (V_5, V_6):
   1) bifid (notched) P-wave in V_5 or V_6, peak interval 0.04 sec. or more; or
   2) impure 2nd peak type in V_5 and/or V_6 and bifid wave in standard leads (I or II), peak interval 0.04 sec. or more
F) Amplitude in V_5 or V_6: 0.11 mV. or more
G) Amplitude in V_6 higher than V_5

Table VII. Incidence of Each Criterion of the P-wave Change
( ) = %

Group →	Normal adults	Hypertension Diastolic blood pressure level (mm. Hg)							Mitral stenosis
		~89	90~99	100~109	110~119	120~129	130~	Total	
No. of cases ↘ Criterion ↓	150	40	68	68	65	34	25	300	100
A	9 (6)	9 (23)	17 (25)	35 (51)	45 (69)	24 (71)	20 (80)	150 (50)	61 (61)
B	15 (10)	8 (20)	16 (24)	30 (46)	26 (40)	25 (73)	19 (76)	124 (41)	89 (89)
C	22 (15)	18 (45)	23 (34)	24 (35)	22 (34)	10 (29)	5 (20)	102 (34)	79 (79)
D	23 (16)	13 (33)	27 (40)	35 (51)	46 (71)	26 (76)	19 (76)	165 (55)	80 (80)
E	15 (10)	5 (13)	20 (30)	43 (63)	52 (80)	32 (94)	24 (96)	176 (59)	90 (90)
F	5 (3)	3 (8)	6 (9)	7 (11)	10 (15)	7 (21)	16 (72)	49 (16)	75 (75)
G	0 (0)	0 (0)	3 (4)	3 (4)	8 (12)	2 (6)	10 (40)	26 (9)	50 (50)

jection of the P-wave.

In this respect, an attempt was made to evaluate the P-wave in both hypertensive and mitral stenosis in a fashion of the cumulative representation of various findings. In this instance, it was supposed that each criterion was equivalent quantitatively but not qualitatively. This permitted to demonstrate the difference between the normal and mitral stenosis clearly as in Fig. 5, where only sporadic change was seen in noraml and its "grade of change" of the P-wave (the sum of criterion appeared in an individual) was less than that of grade II. On the other hand, in mitral stenosis, its grade of change always exceeded grade III. Moreover, in hypertensive cases, there was a definite correlation between the grade of change and the severity of diastolic blood pressure level (Fig. 5; middle). This made a resemblance to mitral stenosis as the diastolic blood pressure rose in severe hypertension. This was also confirmed in 12 follow-up studies of hypertensive cases, where the significant decrease (or increase) in the diastolic blood pressure was always accom-

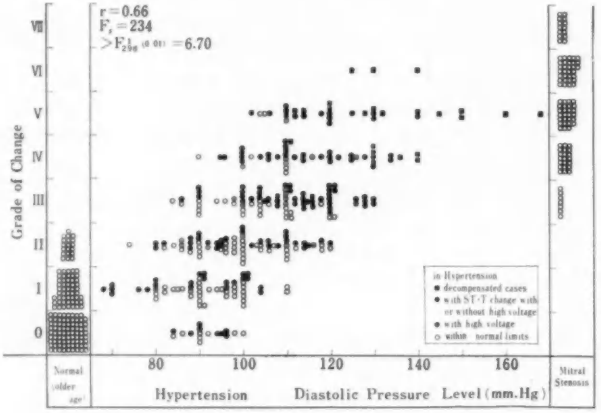

Fig. 5. Relationship of the grade of the P-wave change to the diastolic blood pressure level in 300 cases with hypertension. Control groups consist of 150 cases of normal adults and 100 cases with mitral stenosis. The correlation coefficient in hypertensives is calculated on the assumption that the grade is successive value. Since there are 7 different criteria established, their grade of severity was also devided into 7 groups. Grade 1 to 7 signifies the numbers of P-wave abnormality present, and grade 0 indicates no abnormality of the P-wave.

panied by the decrease (or increase) in the grade of the P-wave change. The same findings were also observed in follow-up cases with mitral stenosis after commissurotomy as previously reported.[28)–30)]

From the results in the present study, it may be concluded that the P-wave of electrocardiogram is a reflection of the physiological status of left atrium in hypertension. With the increase in the diastolic blood pressure in hypertension, the change in the P-wave appeares as in mitral stenosis. This fact suggests that the left atrial overloading in hypertension possibly results from the left ventricular one, which increases with the elevation in the diastolic blood pressure level in hypertension, as described in the succeeding paper.[1)]

Summary and Conclusions

The P-wave in hypertension was studied comparing with that in normal and mitral stenosis.

(1) In various findings of the P-wave, there were significant differences between normal and pathological conditions. Hypertensive cases had intermediate changes compared with the other two groups, and these changes were intensified by the elevation in the diastolic blood pressure level.

(2) From the results obtained in these comparison studies, we proposed the 7 electrocardiographic criteria to assess the changes in the P-wave in both hypertensive and mitral stenosis. In hypertensive cases, the incidence of

each criterion was increased according to the elevation in the diastolic blood pressure level. Special attention was given to some criteria, namely "relative" left axis deviation of the P-wave, which was characteristic to mitral stenosis and mild hypertension, and the finding that the amplitude of the P-wave in lead V_6 was higher than that in V_5, which indicated the more definite sign of the left atrial overloading and often seen in mitral stenosis and severe hypertension.

(3) The grade of P-wave change gave us the more distinctive differentiation of the P-wave between normal and mitral stenosis. In hypertension, this grade was increased with the elevation in the diastolic blood pressure level, and in severe cases, the grade of P-wave change became similar to that seen in mitral stenosis.

(4) On the bases of the observations in the follow-up cases as well as above-mentioned results, we suggested that the change in the P-wave in hypertension was a reflection of the left atrial overloading possibly resulted from the left ventricular one.

References

1. Sakamoto, T., Kaito, G., and Ueda, H.: Jap. Heart J. in press.
2. Lewis, T.: Clinical Electrocardiography, Shaw and Sons, London, 1913.
3. Alexander, A. A., Knight, H. F., and White, P. D.: Arch. Int. Med. **36**: 712, 1925.
4. Winternitz, M.: Med. Klinik **31**: 1575, 1935.
5. Hecht, H.: Deut. Med. Wschr. **63**: 441, 1937.
6. Berliner, K. and Master, A. M.: Arch. Int. Med. **61**: 39, 1938.
7. Trounce, J. R.: Brit. Heart J. **14**: 185, 1952.
8. Reynolds, G.: Brit. Heart J. **15**: 250, 1953.
9. Faser, H. R. I. and Turner, R.: Brit. Heart J. **17**: 459, 1955.
10. Hecht, H. and Woodbury, L. A.: Circulation **2**: 37, 1950.
11. Schmidt, J.: Z. Kreislaufforschg. **41**: 10, 1952.
12. Dines, D. E. and Parkin, T. W.: Proc. Staff Meet. Mayo Clin. **34**: 401, 1959.
13. Macruz, R., Perloff, J. K., and Case, R. B.: Circulation **17**: 882, 1958.
14. Baker, J. M.: The Unipolar Electrocardiogram. A Clinical Interpretation, Appleton-Century-Croft, New York, 1952.
15. Martin de Oliveira, J. and Zimmerman, H. A.: Am. J. Cardiol. **3**: 453, 1958.
16. Lewis, T. and Gilder, M. D.: Phil. Trans. Roy. Soc. **202 B**: 351, 1912. cited by Winternitz (4).
17. White, P. D.: Heart Disease (4. ed.), Macmillan, New York, 1951.
18. Sodi-Pallares, D.: New Bases of Electrocardiography, The C. V. Mosby, St. Louis, 1956.
19. Kossmann, C. E.: Circulation **8**: 920, 1953.
20. White, P. D. and Burwell, C. S.: Arch. Int. Med. **34**: 529, 1924.
21. Schmidt, J.: Z. Kreislaufforschg. **44**: 837, 1955.
22. Sano, T.: Modern Clinical Electrocardiography, Igaku Shoin, Tokyo,

1957 (In Japanese).
23. Conway, J. P., Cronvich, J. A., and Burch, G. E.: Am. Heart J. **38**: 537, 1949.
24. Cabrera, E. and Sodi-Pallares, D.: cited by Sodi-Pallares (18).
25. Thomas, P. and Dejong, D.: Brit. Heart J. **16**: 241, 1954.
26. Oblich, O. and Woodford-Williams, E.: J. Gerontology **8**: 40, 1953.
27. Sano, T., Hellerstein, H. K., and Vayda, E.: Am. Heart J. **53**: 854, 1957.
28. Gibert-Queraltó, J., Torner-Solar, M., and Balaguer-Vintró, I.: Am. Heart J. **49**: 548, 1955.
29. Wenger, R.: cited by Sano (27).
30. Joly, F., Azerad, J., Azerad, N., and Carlotti, J.: Acta cardiol. **13**: 587, 1958.

Electrocardiographic and Phonocardiographic Studies in Hypertension

Part II. Phonocardiographic Study with Special Reference to the Atrial Sound and "Q-1" Interval

Tsuguya SAKAMOTO, M.D., Goro KAITO, M.D., *and* Hideo UEDA, M.D.*

Phonocardiographic study was made in order to display the similarity in the left atrial overloading between hypertension and mitral stenosis which is expressed by the P-wave changes as described in the preceeding paper. It was concluded that the accentuation of the atrial sound and the prolongation of the "Q-1" interval, combined with the P-wave changes, were the reflection of the left atrial overloading, therefore, these findings might be one of the objective signs indicating the impending left heart failure in hypertension.

IN the previous paper,[1] a certain similarity in the P-wave of the electrocardiogram between the cases with hypertension and mitral stenosis was discussed. It was concluded then that this similarity was due to the overloading of the left atrium which appeared in accordance with elevated diastolic blood pressure in hypertension. On the other hand, such a similarity may be also present in the mechanical phenomena in both conditions. In the present study, an attempt was made to evaluate this similarity by means of the phonocardiogram. In addition, the correlation between the electrocardiographic and phonocardiographic findings was also studied.

Methods and Materials

A group of patients was selected from the previous study[1] at random, which consisted of 50 normal, 150 hypertensive and 41 cases with pure mitral stenosis. The follow-up cases and 18 hypertensive cases subjected to cold pressor test were the same in the preceeding report. The cases with widening of QRS complex were excluded.

Using a multi-filter system phonocardiograph, a modification of a system made by Yoshimura[2], a phonocardiogram (PCG) was recorded in these patients. Frequency-response characteristics of the amplifier with 5 filters of this phonocardiograph is shown in Fig. 1. Records were made by moving-coil electromagnetic oscillograph, which had a flat response up to 1,000 cps. With this device, the heart sounds and murmurs with wide frequency range were satisfactorily recorded in any PCG with a suitable filter. Paper speed was 80 mm. and 120 mm. per sec. and these speeds facilitated for the measurement up to 0.01 sec. The dynamic microphone with a chest piece of 35 mm. in diameter was used and it gave a

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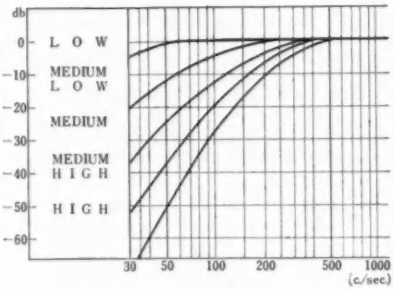


Fig. 1. Frequency-response characteristics of the amplifier. The degree of the attenuation of 50 cps for 500 cps is 0 db in filter 1 (Low), 12.5 db in filter 2 (Medium Low), 25 db in filter 3 (Medium), 37.5 db in filter 4 (Medium High) and 50 db in filter 5 (High). In addition to these five filters, this amplifier is equipped with a filter, which has 62.5 db of attenuation, and it is sometimes used for recording of the particularly high-pitched murmurs. The degree of the same attenuation due to the microphone is 15 db in each PCG.

constant pressure of 200 Gm. to the chest wall. In addition, this phonocardiograph is equipped with a calibration device (5 mV., 50 cps.; alternate current) at the input stage of the amplifier. However, because of many complicating problems on the calibration of the heart sounds, this method was individualized in each subject and was not used for the purpose of comparison in the different cases.

Phonocardiographic recording was taken simultaneously with electrocardiogram (lead II), and when the Q-wave was absent or questionable in this lead, the beginning of the QRS complex was determined by the simultaneous recording of multiple leads (usually 3 standard leads). Records were made with the patients in a supine position at the end of expiration with the glottis open, and at the various auscultatory areas.

Atrial sound: The loudness of the atrial sound was classified according to the difference of PCG, up to which the sound was recognized. For example, grade I was decided when the sound appeared in only Low PCG, and when it was recognized in every PCG, the grade V was decided. Thus, " the grade of accentuation " of atrial sound was classified into 5 groups (from I to V). This method was also used for the comparison of atrial sound in the follow-up cases.

" Q-1 " interval: " Q-1 " interval was measured in the apical Medium PCG by the interval between the Q-wave and the beginning of the first major deflection of the first sound. A special attention was given to determine and differentiate the beginning of the first sound from the ejection component. In cases which showed the diminished first sound and the accentuated ejection sound, this attention was particularly needed. In these instances, it was necessary to compare the Medium PCG with the one of Medium Low and/or Low, which showed a clear cut first sound. Additionally, 50 cases of normal younger persons were used for the comparison study of the " Q-1 " interval.

During cold pressor test, the microphone on the chest wall was firmly fixed, and the gain of the amplifier was maintained constant in order to compare the recordings accurately. The amplitude of the atrial sound was measured on the average of at least 4 in the apical Low PCG before and after the test. No significant change was

seen in the heart rate during this test. T-test was performed for the significance of the analysis.

Results

1) *Atrial sound*:

In a total of 50 normal cases studied, 3 appeared to show the atrial sound up to Medium PCG (grade III). Remaining 47 cases showed

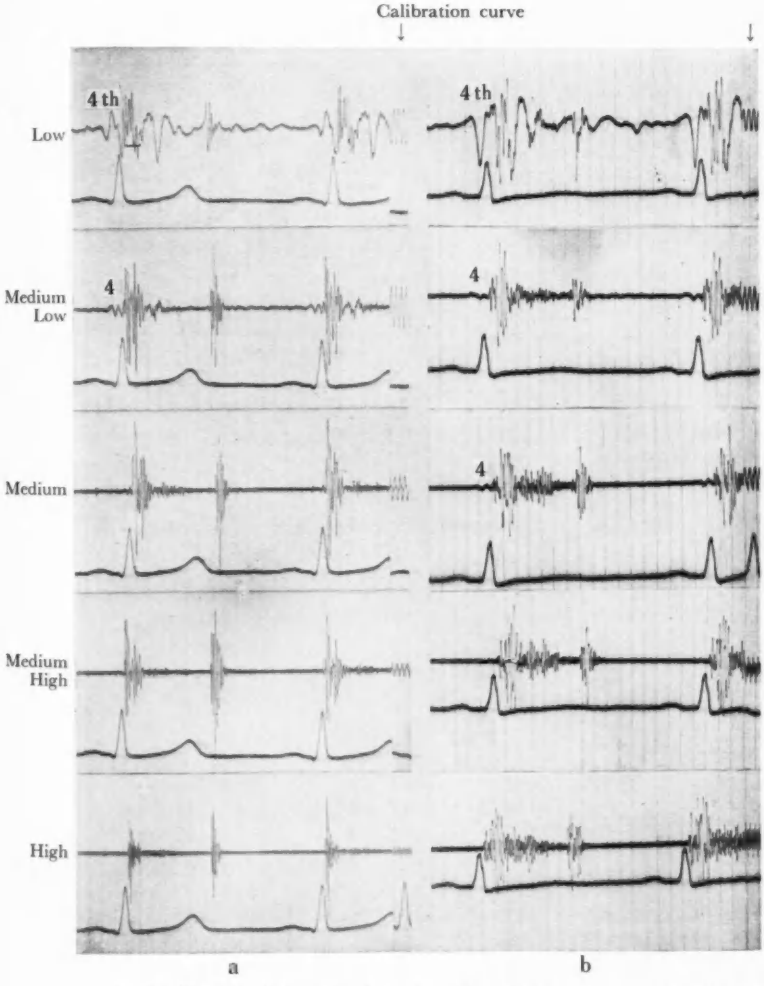


Fig. 2. Phonocardiogram in the cases with mild hypertension (Apex). The atrial sound in the case **a** appears up to Medium Low PCG (grade of accentuation is II). This grade in the case **b** is III.

definite atrial sound in Low PCG (grade I) or up to Medium Low PCG (grade II). On the other hand, the atrial sound in hypertensive became louder and was seen in even the higher characteristic PCG (Figs. 2 and 3). This accentuation of the atrial sound had some correlaton with the diastolic blood pressure as seen in Fig. 4. In 15 hypertensive cases with congestive heart failure, 13 belonged to grade IV or more, and the atrial sound in these cases was audible in all (Fig. 3). The accentuated atrial sound beyond the grade III was usually audible. The maximal intensity of this sound was

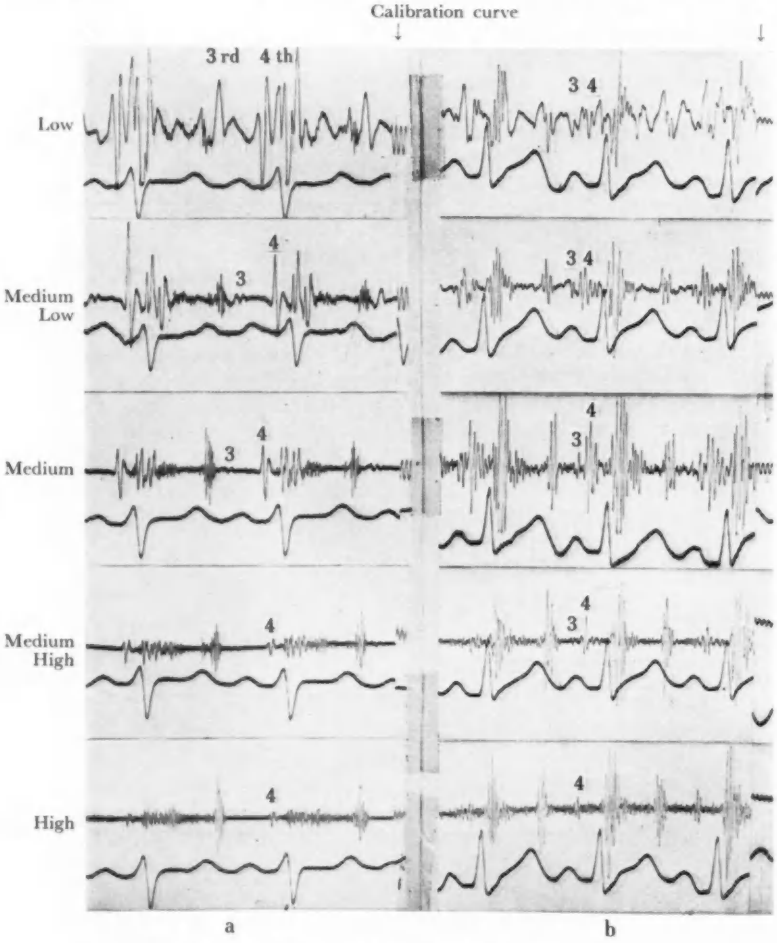


Fig. 3. Phonocardiogram in the cases with severe hypertension (Apex). Quadruple rhythm was heard in both cases. A loud atrial sound appears up to High PCG (grade V). The third sound in hypertension usually appears in the cases with marked decompensation.

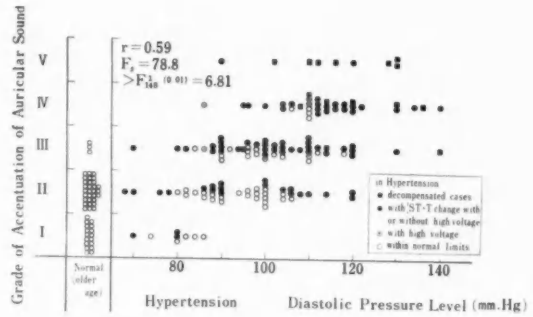


Fig. 4. Relationship between the grade of accentuation of the atrial sound and the diastolic blood pressure level in hypertension. (In succeeding figures, the same symbols are used as to hypertensive cases. The correlation coefficients in this study are calculated on the assumption that the various grades are successive value).

2) " *Q*-1 " *interval*: (Table I)

Table I. Average Value of " Q-1 " Interval

		No. of cases	" Q-1 " interval (sec.)	
Normal adults		50	.051	.050 ± .006
Normal control (younger age)		50	.050	
Hypertension* Diastolic blood pressure level	~ 89 mm. Hg	31	.055	.064 ± .010
	90 ~ 99	30	.060	
	100 ~ 109	35	.066	
	110 ~ 119	34	.068	
	120 ~ 129	11	.073	
	130 ~	9	.075	
Mitral stenosis		41	.081 ± .009	

* decompensated 15 cases .077 ± .010 sec.

at the precordial area in the majority of cases. In only 5 cases, it was heard at the base of the heart alone.

No significant difference was noted in different age group of normal individual ($p>0.05$), and their mean was 0.05 sec. Hypertensive cases occupied the midpoint between normal and mitral stenosis, and its average value was 0.064 sec., which was significantly prolonged from the normal value ($p<0.01$). As the disease progressed, the value of " Q-1 " interval in hypertension became more or less equal to that in mitral stenosis (Fig. 5). This was clearly demonstrated in the cases of hypertension with decompensated

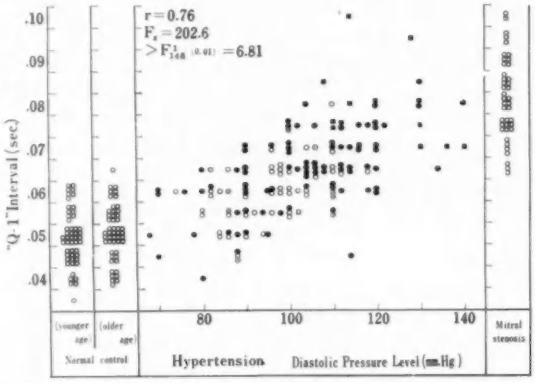
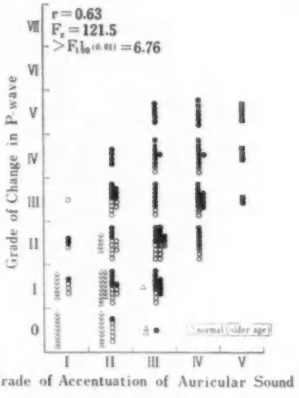


Fig. 5. Relationship of the " Q-1 " interval to the diastolic blood pressure level in hypertension.

3) *Correlation between the phonocardiographic and electrocardiographic findings*:



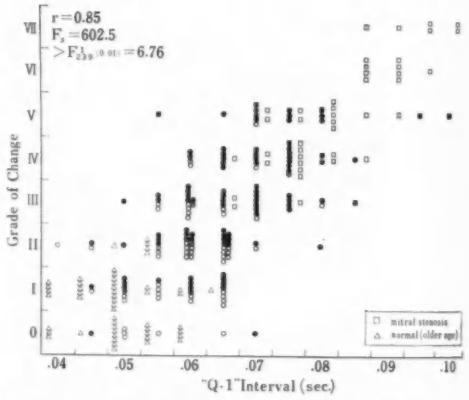


Fig. 6 (Left). Relationship between the grade of accentuation of the atrial sound and the grade of P-wave change.

Fig. 7 (Right). Relationship of the " Q-1 " interval to the grade of P-wave change.

heart, in which the average value of this interval (0.077 sec.) did not differ from that in mitral stenosis ($p>0.05$).

In 150 cases with hypertension and 50 normal cases, there was a parallelism between the loudness of the atrial sound and the grade of P-wave change (Fig. 6). In a total of 241 cases studied, a significant correlation was revealed between the " Q-1 " interval and the grade of the P-wave change (Fig. 7). Their correlation coefficients were 0.54 in hypertension and 0.73 in mitral stenosis. In addition, in 39 cases of mitral stenosis with

opening snap, there was a significant correlation between the grade of the P-wave change and the "2-OS" interval[26] (r=−0.61), and between the grade of P-wave change and the "(Q-1)−(2-OS)" interval[26] (r=0.75). There was also a positive correlation between the "Q-1" interval and the grade of accentuation of the atrial sound (Fig. 8).

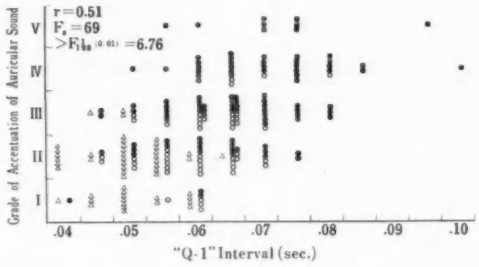


Fig. 8. Relationship of the "Q-1" interval to the grade of accentuation o the atrial sound.

4) *The changes of phonocardiographic findings in the cold pressor test and follow-up study*:

All the cases of hypertensive patients who were subjected to the cold pressor test disclosed the elevation of the diastolic blood pressure for an average of 13 mm. Hg and showed the accentuated atrial sounds during the test (Fig. 9a and b). In some cases, the accentuation of this sound was 5.5 times greater than the control value, and the average value of accentuation of this sound was 2.5 times greater than that of the control. In 2 cases which developed slight bradycardia during the test also revealed the accentuated atrial sound against

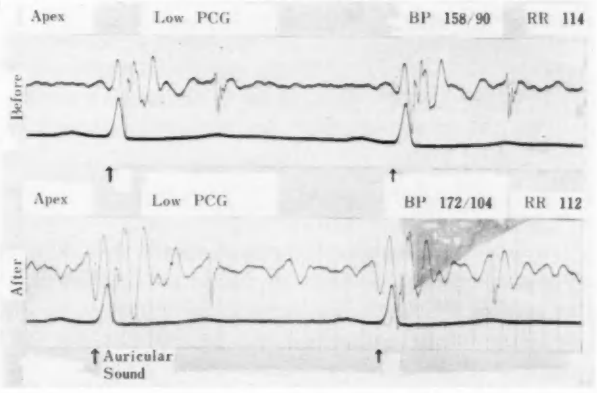


Fig. 9a. Accentuation of the atrial sound caused by the cold pressor test. Marked increase in amplitude of the atrial sound is seen. The other heart sounds also slightly increase in their amplitudes.

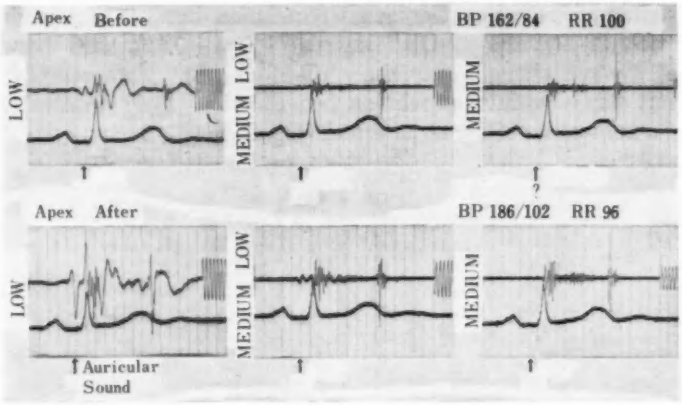


Fig. 9b. Accentuation of the atrial sound caused by the cold pressor test. In addition to the moderate accentuation of the 1st and 2nd heart sound, the atrial sound shows the marked accentuation and appears up to Medium PCG durnig the test. The apical systolic murmur become also louder and definitely audible.

our anticipation. This may indicate that the heart rate has no relationship with the loudness of the atrial sound in our study. Both first and second sounds were also accentuated during the cold pressor test, which would make the usual method for the determination of the loudness of the atrial sound unreliable. The meaning of this will be discussed later. The murmurs, both systolic and daistolic, when they were present, were also accentuated during the test. The change in the P-wave appeared in only 2 severe cases as the diastolic blood pressure rose during the test. In 4 follow-up cases with further elevation of diastolic blood pressure, the change in the P-wave and the accentuated atrial sound became more obvious. In contrary to this finding, 2 cases with markedly improved diastolic blood pressure showed disappearance of audible atrial sound as well as many changes in the P-wave. The similar statement could have been obtained concerning the " Q–1 " interval, and its change was also reflected with the change of the diastolic blood pressure in follow-up studies, but it was impossible to draw any conclusion from the cold pressor test because of short duration of the testing period.

Discussion

Though there have been many investigations on the atrial sound in hypertension,[3)-10)] no definite opinion concerning the physiology of the atrium was seen. In all respects, the results in the present study might give an useful information for the interpretation of the pathophysiology of the atrium in hypertension.

Although an audibility of the atrial sound is influenced by many factors,[11)] the PCG has a merit for the objective representation of this sound. However, there were some difficulties in differentiating the pathological atrial sound from

the physiological one. The usual methods for the differentiation between normal and abnormal atrial sound were obtained from the studies with respect to the difference in their frequency ranges[12)-16)] or the comparison of the amplitudes of the atrial sound with the other heart sounds.[17)-20)] However, the changes of the first and second heart sound could occur by many factors, therefore, these sounds should not be used for the comparison purpose.[21)] On the other hand, the frequency range of the atrial sound can not be determined accurately by the routine phonocardiographic method. For these reasons, we used to determine the grade of accentuated atrial sound by the finding that up to which PCG this sound could be recorded sufficiently. Of course, it may be possible to use greater amplification and to make the appearance of the atrial sound in higher characteristic PCG in which noraml atrial sound can not be recorded with regular amplification. However, this is impossible in our study because almost every case of hypertension has relatively loud second sound at even apical region. Moreover, as it may be seen in the frequency-response characteristics of our amplifier, only loud and/or high frequency atrial sound could be recorded in higher characteristic PCG. Because of these facts, it can be assumed that the atrial sound is accentuated when this sound appears in the higher characteristic PCG. This is well correlated with the diastolic blood pressure in hypertension. In other words, the higher the diastolic blood pressure is, the more the atrial sound is accentuated.

Of course, some technical procedure will influence the intensity of the atrial sound. In order to eliminate this factor and to find that the atrial sound is surely influenced by the change in the diastolic blood pressure, a cold pressor test was carried out. Prior to this test, the microphone was "firmly fixed" to the chest wall and the amplification was regulated at the constant strength. The first recording was made and immediately followed by the second recording during the test. From the results obtained in this test, it was unmistakable that the elevation of the diastolic blood pressure played an important role for the accentuation of the atrial sound. Similar results were also obtained from the follow-up study where the atrial sound appeared in higher characteristic PCG, when there was the increase in the diastolic blood pressure. Then, it may be concluded that the atrial sound is definitely correlated with the diastolic blood pressure level in hypertension.

In follow-up cases, there was the changes of the P-wave in the electrocardiogram besides the louder artial sound due to the increased diastolic blood pressure. However, this change in the P-wave was not evident in an acute experiment in increasing the blood pressure by means in cold pressor test. This would offer an assumption that the change in the P-wave should accompany the sustained elevation of the intra-atrial pressure and some features possibly resulted from the persistent organic changes which might be found in chronic hypertension and not in acute experimentally produced hypertension.

According to Weissler,[22)] there is a prolongation of the "Q-1" interval in hypertension. As far as the factors which cause this prolongation are con-

cerned, Kelly[23] had pointed out two reasons, namely the delay in either electrical or mechanical phenomenon after the onset of the ventricular depolarization. The latter possibility should be applied to explain the prolongation of the " Q-1 " interval in our study because the duration of QRS complex in this study is less than 0.10 sec. Another similar explanation has been given which explains that the delay of the closure of the atrio-ventricular valves is due to insufficient ventricular contraction as seen in the cases with myocarditis.[23] In our study, such cases are well ruled out. The remaining cause is seen in the cases with mitral stenosis. In this instance, the prolongation of the " Q-1 " interval is mainly due to the delay of the mechanical phenomenon, namely due to the delayed closure of the mitral valve caused by the atrio-ventricular pressure gradient, which is caused by the " mechanical block " due to the stenosis of this valve orifice. This mechanism was conclusively affirmed by Braunwald and his associates[24] and Moscovitz and Wilder.[25] Although such a " mechanical block " is not present in hypertension, the possibility may exist that the similar hemodynamic change of the left atrium could be present in both hypertension and mitral stenosis.

The similarity of the circulatory dynamics between the cases with left ventricular failure and mitral stenosis was pointed out by Harvey and his associates,[27] and the common denominator of this similarity was the sustained elevation of the left atrial pressure, as reported by Selzer.[28] From these observations, it is well understood that the " Q-1 " interval in the hypertensive cases with congestive heart failure in our study does not show a significant difference compared with that seen in mitral stenosis. The P-wave changes in the former should be also similar to that in the latter from the same standpoint of view. A loud atrial sound, which is thought to be corresponding with the presystolic murmur in mitral stenosis, might be also produced in the decompensated hypertensive hearts from the same reasons, since no stenosis of the mitral valve orifice is present in hypertensive cases.

Another discussion should be needed to explain the phonocardiographic changes seen in the hypertensive cases without decompensation. It has been noted that the giant " a " wave of the atrial pressure curve is shown in the presence of systolic overloading of the ventricle as in pulmonary[29-31] or aortic[34, 35] stenosis and pulmonary hypertension.[32, 33] Its production mechanism, according to these authors, is based on the change in the pressure-volume elasticity relationships of the ventricle, which results in the elevation of its end-diastolic pressure, thus increased resistance to filling of the ventricle reflects itself in the hypertrophy of the atrium with production of the giant " a " wave. The elevation of the end-diastolic pressure in either ventricle appears before the appearance of the clinically recognizable signs of congestive heart failure.[33, 34] Although the similar finding in the left atrial pressure curve has not been thoroughly investigated in the cases with hypertension, it is likely to assume that there should be the elevated pressure in the left atrium even in the cases of hypertension without decompensation, since

this condition in the atrium produce both the accentuation of the atrial sound and, when it occurs in the left atrium, the prolongation of the " Q-1 " interval. Indeed, the accentuated atrial sound is also seen in the cases with pulmonary stenosis[36] and aortic stenosis[9] in the same fashion as the systemic hypertension (Fig. 10 a and b). Moreover, the prolongation of the " Q-1 " interval is frequently observed in the latter.[37] The P-wave changes in pulmonary stenosis and pulmonary hypertension are well-known, and the P-wave simulating to that seen in mitral stenosis may also be found in severe isolated aortic stenosis (Fig. 10 b). Though the prolonged " Q-1 " interval may enhance

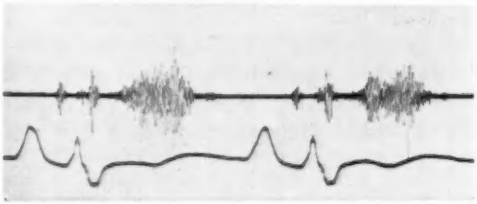


Fig. 10a. Phonocardiogram (Medium High) in a case with pure valvular pulmonary stenosis (Pulmonary area). Loud atrial sound was heard and recognized up to High PCG with its sufficient amplitude. In right heart catheterization, the right ventricular pressure was 150/6 mm.Hg and the characteristic " a " wave was present (the height 13 mm.Hg) in the right atrial pressure curve.

Fig. 10b. Apical phonocardiogram (Medium Low) in a case with pure aortic stenosis without decompensation. An audible atrial sound was recognized up to Medium High PCG. The P-wave is notched. Note the prolongation of the " Q-1 " interval (0.075 sec.).

the tendency to accentuate the atrial sound,[38] these two phonocardiographic findings seemed to be essentially the same manifestations in the hypertensive hearts in our study.

The elevation of the left atrial pressure caused by the elevated left ventricular end-diastolic pressure might be pathophysiologically unavoidable for hypertension. However, if one interprete this phenomenon as the representation of the preparatory stage of left ventricular failure in hypertension, the electrocardiographic and the phonocardiographic findings seen in this study are considered to indicate the " impending " left heart failure, but not heart failure itself, in hypertensive hearts. Then, our results obtained in this study

appeared to be of definite value in the assessment of the severity of the hypertension.

Sammary and Conclusions

Phonocardiographic study was made in order to display the similarity in the left atrial overloading between hypertension and mitral stenosis which is expressed by the P-wave changes as described in the preceeding paper.

(1) A positive correlation among the diastolic blood pressure level and the grade of accentuation of the atrial sound, determined by our multi-filter system phonocardiograph, was revealed and this relation was also ascertained in the follow- up study as well as in the cold pressor test.

(2) " Q-1 " interval in hypertension showed a significant prolongation, and there were definite correlations among this prolongation, the diastolic blood pressure, and the other phonocardiographic and electrocardiographic findings.

(3) The pathophysiological significance of these phonocardiographic and electrocardiographic findings in hypertension was discussed. It was concluded that the accentuation of the atrial sound and the prolongation of the " Q-1 " interval, combined with the P-wave changes, should be the reflection of the left atrial overloadiug, therefore, these findings might be one of the objective signs indicating the impending left heart failure in hypertensive hearts.

References

1. Sakamoto, T., Kaito, G., and Ueda, H.: Jap. Heart J. in press.
2. Yoshimura, S.: Tokyo Jikeikai Med. J. **70**: 79, 1950 (In Japanese).
3. Potain, P. C.: Semaine méd. Paris **20**: 175, 1900.
4. Mozer, J. J. and Duchosal, P.: Arch. mal. coeur **23**: 74, 1930.
5. Duchosal, P.: Am. Heart J. **7**: 613, 1932.
6. Garvin, C. F.: Am. J. Med. Sci. **205**: 814, 1943.
7. Frost, J.: Acta med. scandinav. **134**: 153, 1949.
8. Miles, B. E.: Brit. Heart J. **13**: 327, 1951.
9. Weitzman, D.: Brit. Heart J.: **17**: 70, 1955.
10. Sloan, A. W.: Am. Heart J. **55**: 715, 1958.
11. Duchosal, P.: Arch. mal. couer **28**: 345, 1935.
12. Mannheimer, E.: Acta pediatr. **28**: (Suppl. II) 1, 1940.
13. Carlgren, L. E.: Acta pediatr. **33**: (Suppl. VI) 1, 1946.
14. Luisada, A. A.: The Heart Beat, Graphic Methods in the Study of the Cardiac Patient. Paul B. Hoeber, New York, 1953.
15. Schlitter, J. G. and Schölmerich, P.: Cardiologia **26**: 272, 1955.
16. Luisada, A. A., Richmond, L., and Aravanis, C.: Am. Heart J. **51**: 221, 1956.
17. Luisada, A. A. and Roitman, M.: Arch. Inst. Cardiol. México **17**: 345, 1948. cited by Luisada (14).

18. Sloan, A. W., Campbell, F. W., and Henderson, A. S.: Brit. M. J. **2**: 853, 1952.
19. Engelbertz, P.: Z. Kreislaufforschg. **42**: 364, 1953.
20. Weissel, W.: Z. Kreislaufforschg. **46**: 829, 1957.
21. Ueda, H., Sakamoto, T., Kaito, G., Watanabe, H., Uozumi, Z., Nakajima, A., and Kobayashi, T.: Nippon-Rinshō **17**: 1366, 1959 (In Japanese).
22. Weissler, A. M., Leonard, J. J., and Warren, J. V.: Circulation **18**: 165, 1958.
23. Kelly, J. J., Jr.: Am. J. Med. **19**: 862, 1955.
24. Braunwald, E., Moscovitz, H. L., Amram, S. S., Lasser, R. P., Sapin, S. O., Himmelstein, A., Ravitch, M. M., and Gordon, A. I.: Circulation **12**: 69, 1955.
25. Moscovitz, H. L. and Wilder, R. J.: Am. Heart J. **53**: 741, 1957.
26. Wells, B. G.: Brit. Heart J. **16**: 261, 1954.
27. Harvey, R. J., Ferrer, M. I., Samet, P., Bader, R. A., Bader, M. E., Cournand, A., and Richards, D. W., Jr.: Circulation **9**: 531, 1955.
28. Selzer, A.: Circulation **20**: 243, 1959.
29. Abrahams, D. G. and Wood, P.: Brit. Heart J. **13**: 519, 1951.
30. Maraist, F., Daley, R., Draper, A., Jr., King, J. T., Ferencz, C., and Bing, R. J.: Bull. Johns Hopkins Hosp. **88**: 1, 1951.
31. Engle, M. A. and Taussig, H. B.: Circulation **2**: 481, 1950.
32. Dresdale, D. T., Schultz, M., and Michton, R. J.: Am. J. Med. **11**: 686, 1951.
33. McCord, M. C., Komesu, S., and Blount, S. G.: Am. Heart J. **45**: 706, 1953.
34. Goldberg, H., Dickens, J. D., Raber, G., and Hayes, E. Jr.: Am. Heart J. **53**: 579, 1957.
35. Goldberg, H., Denton, C., Bender, S., and Uricchio, J.: Dis. Chest **33**: 201, 1958.
36. Benchimol, A. and Dimond, E. G.: Circulation **18**: 692, 1958 (Abstract).
37. Sakamoto, T.: Jap. Heart J. to be published.
38. Leonard, J. J., Weissler, A. M., and Warren, J. V.: Circulation **17**: 1007, 1958.

The Quantitative Analysis of Vectorcardiograms of Normal Hearts and Left Ventricular Hypertrophy

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In view of scantiness of quantitative data published up to date in vectorcardiography, it was attempted to supply one from vectorcadiograms of 66 normal subjects and of 42 patients with left ventricular hypertrophy. Apart from features reported by previous authors, the followings were found to be useful for differentiating the two conditions by establishing normal range of values among results of detailed measurement of various portions of the vector loop : anterior magnitude of initial forces and inferior and anterior magnitude of body of QRSsÊ loop were smaller in left ventricular hypertrophy than in normal hearts, and width of body in the frontal plane and posterior magnitude of body of QRSsÊ loop were larger in the former than in the latter.

IN vectorcardiography, quantitative criteria are required for clinical diagnostic purposes as in electrocardiography. In order to establish such criteria, a number of reports must accumulate from a number of laboratories. Qualitative informations of vectorcardiograms of normal subjects and left ventricular hypertrophy cases have been published abundantly up to date.[1)-15)] Several investigators, including the authors,[16)] have reported on measurements of conspicuous parts such as the long axes and the maximal vectors of QRSsÊ loop and TsÊ loop and the difference between the long axis of each loop. It is surprising to know, however, that there has been only one report, i.e. that of Young, Wolff and Chatfield,[17)] so far as we know, which reported on detailed measurements of various parts of the vector loop thus far. Moreover, this report was limited to various measurements of normal vectorcardiograms only and no such report seems to have appeared on abnormal ones. The present study was undertaken to obtain data of detailed measurements on vectorcardiograms of left ventricular hypertrophy as well as of normal subjects on Japanese people obtained by lead systems different from those employed by Young and his associates. Since our previous studies[16)] concerning the qualitative morphological features of normal and abnormal vector loops and some of the quantitative features such as the long axes and the maximal vectors of QRSsÊ loop and TsÊ loop and the difference between the long axis of each loop are essentially in accordance with other studies,[1)-15)] the latter are described briefly and the other quantitative

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aspects are described more in details in the present report.

Vectorcardiograms of marked left ventricular hypertrophy can be distinguished easily from those of normal hearts without any measurement. However, it is not always the case in those of slight ventricular hypertrophy. The purpose of the present study lies in not only obtaining normal values of detailed portion of vector loop but also in obtaining mainly the differential quantitative features of QRSsÊ loop between normal hearts and slight left ventricular hypertrophy. Since the present study did not include a great number of cases, it was not attempted to supply definite criteria, but to supply a material for the criteria.

Materials and Methods

Vectorcardiograms and the standard 12 lead electrocardiograms were obtained on 66 normal subjects and 42 patients with left ventricular hypertrophy. The greater parts of the former were healthy medical students and those of the latter were selected from a total of 390 senile cases over 60 years of age who were examined for mass survey. The age distribution was shown in Table I. In all cases, histories were

Table I. Age Distribution of the Materials

		Number of cases					
Age		20~29	30~39	40~49	50~59	60~69	70~79
Nomal	male	26	3	3	2	9	7
	female	2	1	3	0	4	6
Left ventricular hypertrophy	male	2	2	2	4	13	3
	female	1	0	1	2	9	3

taken carefully and physical examinations including blood pressure measurement were made. In most cases of suspected left ventricular hypertrophy, serum cholesterol and serum lipoprotein were measured, in addition to the ophthalmoscopic examination and urinalysis. In these cases 60 mm. single chest photofluorograms of P–A and left oblique projections were also taken. The causes of the left ventricular hypertrophy were mostly hypertensive and/or sclerotic heart diseases.

In almost all the cases, vectorcardiograms were obtained by two methods, i.e. by that of Frank[18] and that of Grishman and associates.[7] In 9 cases of normal and 6 cases of left ventricular hypertrophy, only the Frank method was used and in other 2 cases of normal and 6 cases of left ventricular hypertrophy, vectorcardiograms were recorded by the Grishman method only. For purposes of comparison, the left sagittal planar projection was obtained in either method instead of right one of original method of Grishman by changing polarity of the sagittal lead of that projection. In all cases three planar projections were simultaneously recorded in 1 film. All the results of the examinations were carefully considered in deciding the subjects as normal or of left ventricular hypertrophy with the aid of the electrocardiograms and photofluorograms particularly.

Results

The description and the method for the measurements of the parts of the vector loop were similar to that of Young and associates[17] except for the following: (1) Width of the body in the frontal projection was measured as that of the whole of the body instead of width of its left part. (2) The measurement of ' appendage ' (M in Fig. 3 of reference 2) and width of the terminal appendage were discarded, in order to make measurements as even as possible in all projections. Our method of measurement for overall length of loop was as illustrated in Fig. 1, which was not sufficiently clear in the horizontal

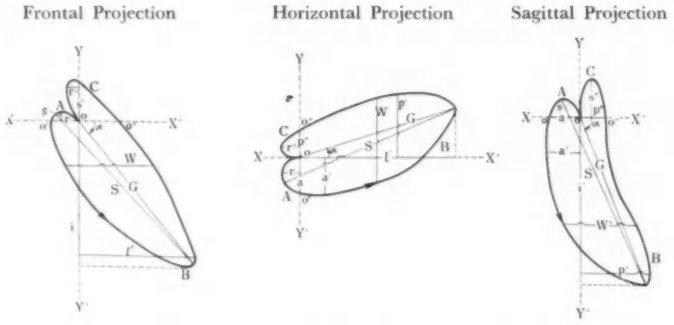

Fig. 1. Nomenclature and explanation of measurement. O at the point of intersection of XX′ and YY′ equals the point of origin of the cardiac vector. Initial forces equal the trace starting at O and ending at O′. Body equals the trace starting at O′ and ending at O″. Terminal appendage equals the trace starting at O″ and ending at O. G equals maximal vector. Long axis equals angle subtended by maximal vector (G) and XX′. S=overall length of loop, W=width of body. a=anterior, p=posterior, s=superior, i=inferior, l=left, r=right: They are the perpendicular projections of maximal dimension of initial forces, body and terminal appendage, the latter two of which are indicated by ′ and ″, respectively.

and sagittal projections in their original. When the initial forces were absent, the maximal vector was substituted for the overall length of the loop.

All the results of our measurement were tabulated in Tables II and III and some important factors of the measurements were shown graphically in Fig. 2.

Only a few remarks are necessary for explaining these tables. From the values of the long axis of the QRS loop in Tables II and III it is shown that the maximal vector of the left ventricular hypertrophy tended to direct more leftwards, superiorly and posteriorly. The average value of magnitude of the maximal vector was slightly larger in left ventricular hypertrophy than in normal hearts, but overlapping of values in both groups was much greater than expected. Since the overall average did not express the situation well, the distribution was shown in Fig. 3. The initial forces and the terminal appendage were occasionally absent. Their presence or absence in the frontal

Table II. Measurements of the QRS Loop of Normal Hearts

	Normal	Frontal									
		Frank method					Grishman method				
		Mean	Median	±S.D.	Sm.	La.	Mean	Median	±S.D.	Sm.	La.
(deg.)	Long axis	38.7	46.5	15.0	9.0	94.1	35.2	45.0	9.85	7.0	60.0
(mV.)	Max. vector	1.20	1.11	0.18	0.47	2.25	1.06	0.96	0.17	0.48	1.65
I	Superior	0.06	0.09	0.04	0.1	0.39	0.04	0.04	0.003	0.005	0.20
F	Right*	0.04	0.04	0.03	0.01	0.26	0.09	0.09	0.06	0.02	0.21
(mV.)	Duration (msec.)	6.0	7.0	2.3	2.0	28.0	6.0	8.0	2.0	2.0	30.0
T	Superior	0.07	0.11	0.06	0.01	0.56	0.04	0.06	0.04	0.005	0.28
A	Right	0.19	0.15	0.07	0.01	0.80	0.03	0.05	0.05	0.005	0.31
(mV.)	Duration (msec.)	8.0	10.0	3.5	2.0	36.0	9.0	16.0	2.0	6.0	52.0
B	Width	0.51	0.48	0.18	0.05	1.26	0.15	0.20	0.21	0.005	0.63
	Inferior	0.98	0.91	0.19	0.10	1.88	0.63	0.68	0.15	0.05	1.07
(mV.)	Left	1.08	1.05	0.28	0.34	2.06	0.89	0.87	0.35	0.32	1.61
	Length	1.20	1.11	0.18	0.47	2.25	1.06	0.96	0.17	0.48	1.65
R A T I O	Width (B) / Length (B)	0.41	0.36	0.21	0.01	1.19	0.29	0.27	0.21	0.01	1.00
	Length (IF) / Length (B)	0.07	0.08	0.11	0.01	0.57	0.06	0.08	0.07	0.01	0.41
	Superior (TA) / Inferior (B)	0.14	0.11	0.44	0.01	3.40	0.26	0.33	0.85	0.01	6.00
(mV.)	Overall length of loop	1.28	1.16	0.28	0.48	2.64	1.16	0.99	0.25	0.48	1.84

	Normal	Horizontal									
		Frank method					Grishman method				
		Mean	Median	±S.D.	Sm.	La.	Mean	Median	±S.D.	Sm.	La.
(deg.)	Long axis	-4.5	2.0	29.5	-90.0	35.5	0.8	-5.0	22.7	-28.0	31.5
(mV.)	Max. vector	1.15	1.11	0.29	0.36	2.26	0.98	0.90	0.37	0.28	1.55
I	Right	0.03	0.05	0.03	0.01	0.28	0.10	0.09	0.08	0.002	0.17
F	Anterior	0.23	0.25	0.11	0.05	0.78	0.18	0.11	0.10	0.02	0.40
(mV.)	Duration (msec.)	8.0	10.0	1.5	2.0	24.0	12.0	14.0	4.7	4.0	32.0
T	Right	0.15	0.17	0.08	0.01	0.80	0.03	0.04	0.04	0.005	0.21
A	Posterior	0.24	0.28	0.15	0.01	0.58	0.13	0.14	0.07	0.01	0.43
(mV.)	Duration (msec.)	20.0	28.0	8.0	10.0	52.0	12.0	21.0	4.7	6.0	58.0
B	Width	1.04	0.99	0.27	0.25	2.16	0.45	0.33	0.25	0.07	0.81
	Anterior	0.55	0.60	0.14	0.10	1.22	0.17	0.14	0.06	0.05	0.42
(mV.)	Posterior	0.76	0.74	0.05	0.15	1.98	0.25	0.24	0.08	0.01	0.62
	Left	1.04	0.99	0.28	0.35	2.01	0.81	0.88	0.20	0.28	1.51
R A T I O	Width (B) / Left (B)	1.07	1.05	0.66	0.18	1.87	0.36	0.40	0.24	0.03	1.17
	Right (IF) / Left (B)	0.07	0.09	0.11	0.007	0.66	0.10	0.11	0.15	0.01	0.88
	Right (TA) / Left (B)	0.19	0.10	0.39	0.01	2.00	0.08	0.08	0.17	0.006	0.80
(mV.)	Overall length of loop	1.27	1.22	0.19	0.39	2.52	1.06	1.00	0.25	0.44	1.82

		Normal	Sagittal									
			Frank method					Grishman method				
			Mean	Median	±S.D.	Sm.	La.	Mean	Median	±S.D.	Sm.	La.
(deg.)	Long axis		54.3	68.0	27.0	23.0	99.0	78.4	88.0	22.4	32.0	98.7
(mV.)	Max. vector		1.04	0.99	0.23	0.29	2.27	0.68	0.66	0.20	0.24	1.21
I	Superior		0.07	0.09	0.04	0.01	0.36	0.04	0.03	0.02	0.01	0.26
F	Anterior		0.24	0.22	0.12	0.05	0.79	0.16	0.11	0.11	0.04	0.31
(mV.)	Duration (msec.)		12.0	14.0	4.7	6.0	28.0	8.0	10.0	1.5	4.0	24.0
T	Posterior		0.26	0.26	0.14	0.01	1.54	0.14	0.11	0.01	0.01	0.48
A	Superior		0.08	0.11	0.07	0.01	0.57	0.04	0.05	0.09	0.001	0.27
(mV.)	Duration (msec.)		11.0	16.0	4.3	2.0	50.0	10.0	16.0	4.0	4.0	44.0
B	Width		0.91	0.87	0.29	0.20	2.14	0.35	0.20	0.17	0.02	0.59
	Anterior		0.55	0.65	0.19	0.05	1.30	0.14	0.12	0.04	0.03	0.45
(mV.)	Posterior		0.76	0.72	0.18	0.10	2.18	0.25	0.21	0.07	0.01	0.58
	Inferior		0.77	0.78	0.20	0.10	1.97	0.64	0.60	0.37	0.03	1.08
R A T I O	Width (B) / Inferior (B)		1.30	1.06	0.88	0.02	4.06	0.37	0.39	0.46	0.07	2.00
	Superior (IF) / Inferior (B)		0.07	0.09	0.07	0.03	0.35	0.05	0.07	0.08	0.01	0.28
	Superior (TA) / Inferior (B)		0.12	0.12	0.29	0.01	1.97	0.13	0.21	0.25	0.007	1.12
(mV.)	Overall length of loop		1.23	1.12	0.46	0.32	2.49	0.75	0.70	0.39	0.24	1.48

B=Body; IF=Initial force; TA=Terminal appendage; Sm.=Smallest observation; La.=Largest observation; S.D.=Standard deviation; deg.=degree.

When the initial forces or the terminal appendages were absent, they were calculated as zero to obtain the mean and median, but these zero values were excluded as the smallest observation.

* When there were no rightward components of the initial forces or of the terminal appendage, their right magnitude was measured as zero. Since in the frontal plane normal QRS loop inscribed more frequently clockwise, measurement of rightward magnitude alone gave frequently irrational impression. When the right magnitude of the initial forces in the frontal plane was measured as plus and the left one as minus, mean, median, s.d., sm. and la. were 0.01, 0.04, ±0.15, −1.08 and 0.28 respectively by the Frank method, and 0.02, 0.08, ±0.01, −0.72 and 0.28 by the Grishman method.

projection was greatly influenced by the direction of the initial portion of the QRSsÊ loop and by the direction of its inscription, which were summarized in Table IV.

From the results in Tables II and III and in Fig. 2, it is realized that some of the factors are useful for the differentiation of the two conditions. Namely, anterior magnitude of initial forces and inferior magnitude of body were generally smaller in cases of left ventricular hypertrophy than in normal hearts. The differences were greater in the QRS loop by the Frank method

Table III. Measurements of the QRS Loop of Left Ventricular Hypertrophy

Left ventricular hypertrophy		Frontal									
		Frank method					Grishman method				
		Mean	Median	±S.D.	Sm.	La.	Mean	Median	±S.D.	Sm.	La.
(deg.)	Long axis	25.0	29.0	27.7	-1.0	56.0	23.7	22.9	14.8	3.6	44.5
(mV.)	Max. vector	1.34	1.23	0.31	0.68	3.25	1.12	0.92	0.27	0.48	2.12
I	Superior	0.03	0.05	0.02	0.01	0.14	0.08	0.07	0.11	0.01	0.84
F	Right*	0.08	0.05	0.07	0.01	0.22	0.04	0.06	0.04	0.01	0.28
(mV.)	Duration (msec.)	8.2	10.0	1.21	4.0	24.0	8.0	9.0	1.1	4.0	26.0
T	Superior	0.12	0.12	0.08	0.02	0.47	0.06	0.08	0.03	0.005	0.33
A	Right	0.08	0.06	0.06	0.01	0.34	0.05	0.06	0.02	0.03	0.36
(mV.)	Duration (msec.)	18.0	22.0	3.1	4.0	53.0	13.4	16.0	3.35	5.0	30.0
B	Width	0.54	0.50	0.15	0.05	1.49	0.91	0.85	0.34	0.01	1.36
	Inferior	0.52	0.52	0.17	0.12	1.42	0.50	0.52	0.15	0.04	1.49
(mV.)	Left	1.21	1.18	1.31	0.48	3.22	0.92	0.88	0.26	0.21	1.61
	Length	1.34	1.23	0.31	0.68	3.25	1.12	0.92	0.27	0.48	2.12
RATIO	Width (B) / Length (B)	0.45	0.39	0.28	0.01	1.11	0.38	0.48	0.57	0.009	1.03
	Length (IF) / Length (B)	0.06	0.13	0.11	0.01	0.50	0.02	0.11	0.06	0.06	0.27
	Superior (TA) / Inferior (B)	0.14	0.11	0.23	0.01	0.89	0.22	0.28	0.31	0.01	1.12
(mV.)	Overall length of loop	1.45	1.23	0.36	0.72	3.68	1.17	0.99	0.25	0.48	2.14

Left ventricular hypertrophy		Horizontal									
		Frank method					Grishman method				
		Mean	Median	±S.D.	Sm.	La.	Mean	Median	±S.D.	Sm.	La.
(deg.)	Long axis	-22.6	-28.9	31.5	-113.5	7.0	-26.0	-23.0	10.5	-37.0	26.0
(mV.)	Max. vector	1.42	1.24	0.37	0.55	3.19	1.05	0.99	0.42	0.34	2.31
I	Right	0.08	0.05	0.05	0.01	0.20	0.05	0.08	0.13	0.005	0.70
F	Anterior	0.05	0.07	0.04	0.02	0.22	0.08	0.10	0.06	0.07	0.29
(mV.)	Duration (msec.)	6.2	7.0	2.7	5.0	24.0	9.2	12.0	3.67	2.00	41.6
T	Right	0.10	0.08	0.07	0.01	0.31	0.02	0.03	0.04	0.005	0.36
A	Posterior	0.40	0.37	0.12	0.05	1.30	0.16	0.13	0.17	0.06	1.24
(mV.)	Duration (msec.)	18.8	22.0	7.1	3.0	46.2	5.6	15.0	2.23	4.0	36.0
B	Width	1.21	0.94	0.21	0.34	3.44	0.54	0.42	0.09	0.05	1.40
	Anterior	0.42	0.40	0.19	0.08	1.12	0.04	0.07	0.02	0.005	0.49
(mV.)	Posterior	0.96	0.94	0.16	0.34	2.98	0.45	0.44	0.13	0.03	1.52
	Left	1.26	1.18	0.25	0.44	3.16	1.02	0.95	0.29	0.31	1.66
RATIO	Width(B) / Left (B)	1.02	0.96	0.41	0.29	1.99	0.34	0.25	0.19	0.02	0.78
	Right (IF) / Left (B)	0.03	0.08	0.05	0.007	0.22	0.06	0.09	0.14	0.001	0.81
	Right (TA) / Left (B)	0.13	0.10	0.31	0.01	0.64	0.05	0.80	0.16	0.001	0.96
(mV.)	Overall length of loop	1.54	1.26	0.32	0.88	3.76	1.14	1.02	0.27	0.44	2.41

Left ventricular hypertrophy		Sagittal									
		Frank method					Grishman method				
		Mean	Median	±S.D.	Sm.	La.	Mean	Median	±S.D.	Sm.	La.
(deg.)	Long axis	30.2	26.3	14.4	-18.0	98.5	40.0	54.4	0.32	-12.0	96.5
(mV.)	Max. vector	1.12	1.11	0.24	0.48	3.20	0.72	0.69	0.25	0.21	1.62
I	Superior	0.03	0.03	0.02	0.01	0.12	0.02	0.02	0.01	0.005	0.54
F	Anterior	0.04	0.04	0.01	0.01	0.15	0.02	0.03	0.02	0.02	0.35
(mV.)	Duration (msec.)	17.6	18.0	2.9	6.0	28.0	13.6	16.0	1.34	10.0	22.0
T	Posterior	0.33	0.43	0.03	0.02	1.34	0.12	0.18	0.03	0.005	0.78
A	Superior	0.12	0.13	0.03	0.02	0.51	0.06	0.07	0.04	0.01	0.38
(mV.)	Duration (msec.)	18.1	22.0	4.4	9.0	83.0	18.2	18.0	3.27	4.0	53.2
B	Width	1.01	0.97	0.27	0.35	2.46	0.34	0.31	0.03	0.05	0.98
	Anterior	0.41	0.35	0.16	0.02	1.11	0.06	0.06	0.01	0.005	0.16
(mV.)	Posterior	0.91	0.94	0.09	0.35	3.00	0.44	0.42	0.03	0.05	1.40
	Inferior	0.50	0.57	0.13	0.10	1.38	0.44	0.40	0.17	0.05	1.24
R A T I O	Width (B) / Inferior (B)	1.50	1.72	0.83	0.18	3.50	0.62	0.55	0.16	0.11	2.20
	Superior (IF) / Inferior (B)	0.06	0.11	0.15	0.01	0.57	0.05	0.10	0.01	0.02	0.80
	Superior (TA) / Inferior (B)	0.18	0.15	0.17	0.04	1.00	0.17	0.33	0.27	0.03	1.00
(mV.)	Overall length of loop	1.30	1.13	0.24	0.53	3.68	0.81	0.72	0.26	0.21	1.82

The abbreviations and treatment of absence of the initial forces or the terminal appendage were the same as in Table II.

* When the right magnitude of the initial forces in the frontal plane was measured as plus and the left one as minus, mean, median, s.d., sm. and la. were −0.02, −0.20, ±0.23, −1.16 and 0.37 by the Frank method, and 0.03, 0.06, ±0.18, −0.82 and 0.16 by the Grishman method.

than by the Grishman method. Both of these items constitute a good diagnostic differentiation in vector loops by the Frank method. In vector loops by the Grishman method, anterior magnitude of body was usually smaller in cases with left ventricular hypertrophy than in normal hearts, which is useful for differentiation, but in vector loops by the Frank method there was too much overlapping.

Superior magnitude of terminal appendage, left and posterior magnitude, width and length of body and overall length of QRS loop showed a tendency to be larger in left ventricular hypertrophy cases than in normal hearts. Among these, width of body in frontal plane vector loops by the Grishman method and posterior magnitude of body by either method constitute a good diagnostic differentiation because of less overlapping.

Duration of the initial forces and the terminal appendage tended to be larger in the frontal plane and the sagittal plane but to be slightly smaller in

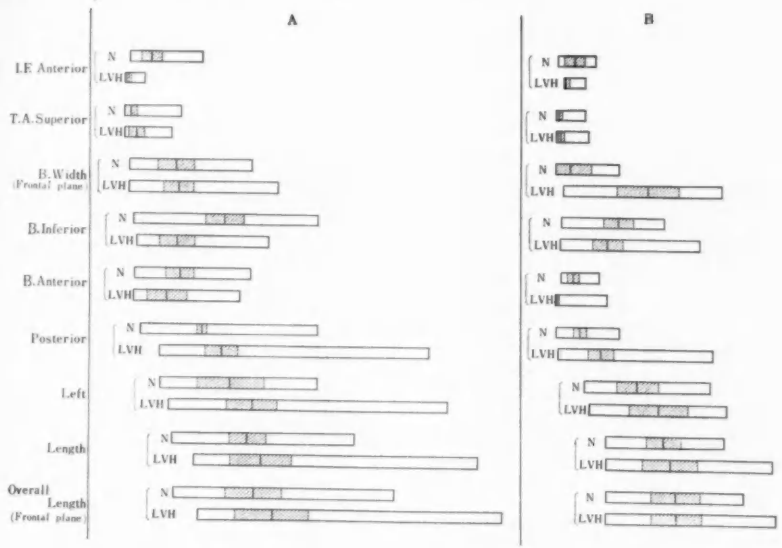

Fig. 2. Graphical presentation of magnitude of various factors. Open columns indicate ranges from the smallest observation to the largest one. Cross-hatched columns represent the standard deviation. Block lines in the middle represent the mean.

A: the results by the Frank method; B: the results by the Grishman method; N=normal, LVH=left ventricular hypertrophy.

Table IV. Direction of Inscription and of Initial Portion of QRS Loop in the Frontal Plane

		Number of cases			
		Frank method		Grishman method	
		Normal	Left ventricular hypertrophy	Normal	Left ventricular hypertrophy
Direction of inscription	Clockwise	41	9	28	9
	Clockwise, terminally counterclockwise	13	4	17	5
	Counterclockwise, terminally clockwise	5	6	6	5
	Counterclockwise	5	17	6	17
Direction of initial portion	Right superior	9	1	10	1
	Right inferior	19	26	18	24
	Left superior	33	0	25	0
	Left inferior	3	9	4	11

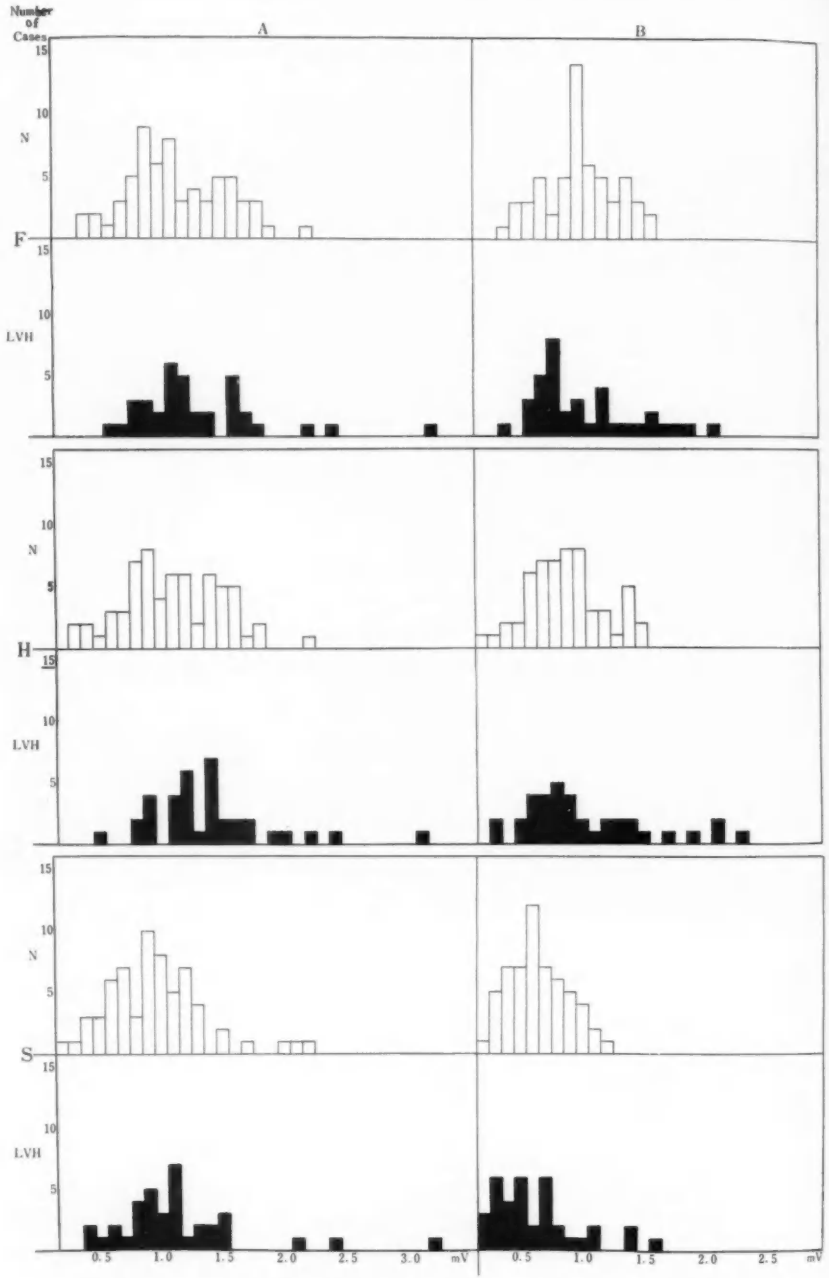

Fig. 3. The magnitude of QRS maximal vector. Ordinates represent number of individuals, abscissae, the maximal vectors.

A: the results by the Frank method; B: the results by the Grishman method. N=normal, LVH=left ventricular hypertrophy, F=frontal projections, H=horizontal projections, S=sagittal projections.

the horizontal plane in left ventricular hypertrophy than in normal hearts.

Many of the above-mentioned characteristics are shown in examples of Fig. 4.

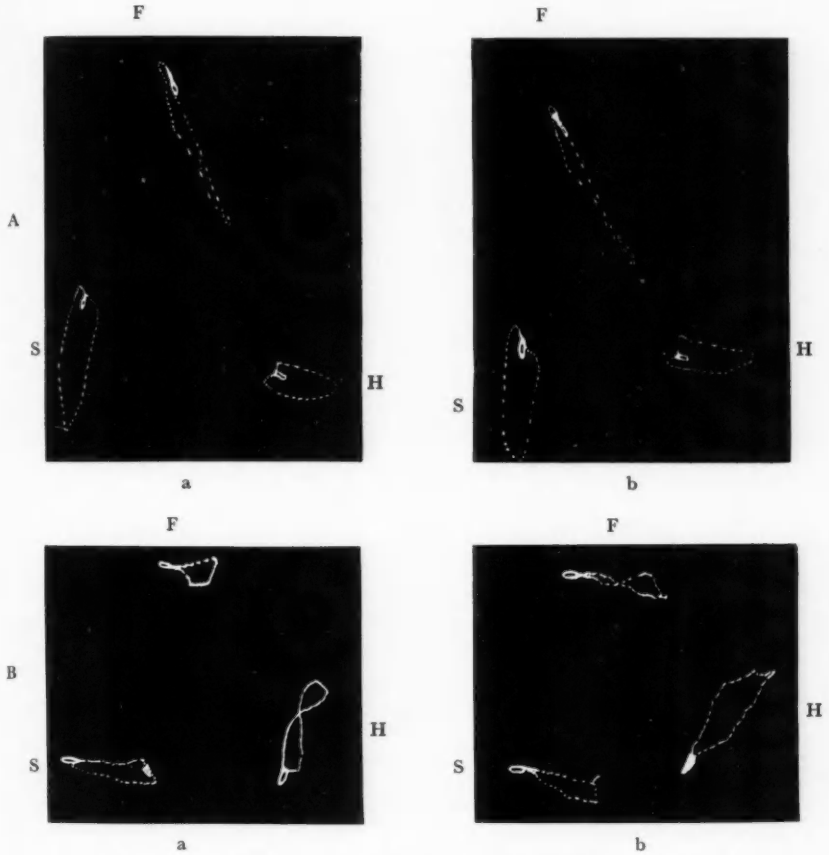

Fig. 4. Vectorcardiograms of a normal subject (A) and of marked left ventricular hypertrophy (B). Each one example taken by the two methods, i.e. by the Frank method (a) and by the Grishman method (b).
F=frontal plane, H=horizontal plane, S=sagittal plane.

As for the TsÊ loop and the ST vector, measurements were made only in their major factors as had been by Young and associates. Because the results on these materials were essentially the same as our previous study,[1] only their essence was listed in Table V without further comments.

Discussion

It was rather unexpected to find that the difference of the magnitude of

Table V. Measurements of Maximal Vector and Long Axis of T loop.

			T loop length (mV.)				
			Mean	Median	Standard deviation	Smallest observation	Largest observation
Frank method	Normal	Frontal	0.42	0.55	±0.16	0.14	0.83
		Horizontal	0.42	0.41	±0.22	0.14	0.81
		Sagittal	0.40	0.42	±0.18	0.07	0.90
	Left ventricular hypertrophy	Frontal	0.24	0.21	±0.11	0.07	0.63
		Horizontal	0.31	0.28	±0.16	0.07	0.63
		Sagittal	0.31	0.28	±0.15	0.07	0.55
Grishman method	Normal	Frontal	0.25	0.24	±0.01	0.12	0.39
		Horizontal	0.23	0.24	±0.01	0.12	0.39
		Sagittal	0.20	0.16	±0.01	0.08	0.39
	Left ventricular hypertrophy	Frontal	0.14	0.14	±0.01	0.01	0.32
		Horizontal	0.15	0.12	±0.01	0.01	0.39
		Sagittal	0.14	0.12	±0.008	0.01	0.28

* A positive value indicates that the T axis is anterior or to the right (frontal plane) of QRS.

the maximal vector between normal hearts and cases with left ventricular hypertrophy was not so great, especially in the QRSsÊ loop by the Grishman method. The average value of this magnitude of the QRS loop by the Frank method was considerably greater in left ventricular hypertrophy than in normal, but overlapping of values was still too great for regarding it as a good differentiating criterion. One of the reasons is due to the fact that many cases of left ventricular hypertrophy were selected from the materials of a mass survey, and that cases with mild and moderate left ventricular hypertrophy were included in greater proportion. This was performed purposely, since our aim lay in finding diagnostic criteria for differentiating normal from slight left ventricular hypertrophy. Therefore, this finding means that in vectorcardiography increase in the magnitude of the maximal vector could not be regarded as one of the earliest signs of left ventricular hypertrophy, so far as this series was concerned, which does not entirely correspond to the well-known fact in electrocardiography that increase in the magnitude of the QRS deflection appeared in the earliest stage of the left ventricular hypertrophy.

The Difference (Angle) between the Long Axis of the QRS and T Loop.

Long axis of T loop (deg.)					Difference between long axis of T and QRS (deg.)*				
Mean	Median	Standard deviation	Smallest observation	Largest observation	Mean	Median	Standard deviation	Smallest observation	Largest observation
44.5	46.0	±14.6	4.0	79.0	+ 14.1 − 8.5	+ 13.0 − 7.0	±11.8 ± 6.6	+ 1.0 − 1.0	+ 52.0 − 34.0
39.0	46.0	±23.4	−28.0	90.0	+ 53.3 − 17.8	+ 49.0 − 12.0	±31.6 ±12.6	+ 2.0 − 1.0	+142.0 − 34.0
133.8	141.0	±27.5	24.0	173.0	+ 66.5 − 13.6	+ 62.0 − 15.0	±33.4 ±10.5	+ 1.0 − 3.0	+151.0 − 31.0
126.0	160.0	±74.5	−163.0	180.0	+105.1 − 77.6	+141.0 − 88.0	±59.2 ±80.6	+ 8.0 − 9.0	+180.0 −159.0
95.6	97.0	±69.9	1.0	173.0	+144.3 − 93.5	+130.0 − 93.5	±61.4 ——	+20.0 −19.0	+173.0 −168.0
170.2	179.0	±36.9	−173.0	180.0	+145.8 − 67.3	+150.0 − 67.3	±96.4 ——	+56.0 − 4.0	+179.0 −180.0
39.5	40.0	±14.9	4.0	90.0	+ 8.8 − 5.3	+ 6.0 − 7.0	± 8.0 ± 7.3	+ 1.0 − 1.0	+ 49.0 − 29.0
9.4	10.0	±18.6	27.0	100.0	+ 19.4 − 8.5	+ 16.0 − 9.0	±22.7 ± 4.5	+ 1.0 − 2.0	+141.0 − 19.0
102.4	104.0	±13.5	9.0	151.0	+ 25.9 − 8.5	+ 26.0 − 7.0	±25.1 ± 5.9	+ 1.0 − 1.0	+ 92.0 − 23.0
118.2	138.0	±69.8	−162.0	177.0	+101.1 − 40.5	+113.0 − 48.0	±69.1 ±50.2	+ 1.0 − 2.0	+178.0 −127.0
164.9	165.0	±95.0	−178.0	174.0	+114.4 − 68.0	+138.0 − 63.0	±63.0 ±71.0	+ 6.0 − 1.0	+179.0 −170.0
135.9	157.0	±88.7	−180.0	179.0	+100.2 −113.0	+113.0 −140.0	±55.2 ±55.4	+11.0 − 1.0	+180.0 −170.0

Statistics were made separately in positive value groups and in negative value groups.

Summary

(1) Measurement of various portions of vector loop obtained from 66 normal subjects and 42 patients with left ventricular hypertrophy was made. Vectorcardiograms were taken by the Frank method and by the Grishman method. In addition to normal values, differential quantitative features between two conditions not reported thus far were endeavoured to be sought.

(2) In general anterior magnitude of initial forces and inferior and anterior magnitude of body of QRSsÊ loop were smaller in left ventricular hypertrophy than in normal, and width of the body in frontal plane and posterior magnitude of the body were larger in the former than in the latter. These items constitute useful diagnostic differentiation between both conditions because of less overlapping.

(3) The magnitude of the maximal vector of the QRSsÊ loop had tendency to be larger in cases with left ventricular hypertrophy than in normal

hearts, but the overlapping between both values was too great for a good differential criterion.

References

1. Duchosal, P.W. and Sulzer, R.: La Vectocardiographie, Karger, Basle, 1949.
2. Jouve, A. and Buisson, P.: La Vectocardiographie en Clinique, Masson et Cie, Paris, 1950.
3. Donzelot, E., Milovanovich, J.B., and Kaufmann, H.: Etudes Pratiques de Vectocardiographie, L' Expansion Scientifique Française, 1950.
4. Scherlis, L. and Grishman, A.: Am. Heart J. **41**: 494, 1951; Scherlis, L., Lasser, R.P., and Grishman, A.: Am. Heart J. **42**: 235, 1951.
5. Den Boer, W.: Vectorcardiographie Drukkery. Kemink en Zoon N.V., Utrecht, 1951.
6. Portheine, H.: Verhandl. deutsch. Gesellsch. Kreislaufforsch. **18**: 196, 1952.
7. Grishman, A. and Scherlis, L.: Spatial Vectorcardiography, W.B. Saunders Company, Philadelphia, 1952.
8. Burch, G.E., Abildskov, J.A., and Cronvich, A.A.: Spatial Vectorcardiography, Lea & Febiger, Philadelphia, 1953.
9. Podio, R.B.: Arch. mal. coeur **46**: 728, 1953.
10. Wenger, R.: Klinische Vektorkardiographie, Verlag von Dr. Dietrich Steinkopff, Darmstadt, 1956.
11. Fowler, N.O. and Helm, R.A.: Am. Heart J. **46**: 821, 1953.
12. Horan, L.G., Burch, G.E., Abildskov, J.A., and Cronvich, J.A.: Circulation **10**: 728, 1954.
13. Abildskov, J.A.: Circulation **12**: 286, 1955.
14. Lamb, L.E., Grosgurin, J.R., and Duchosal, P.W.: Cardiologia **28**: 65 (Fasc. 2), 1956.
15. Nimura, Y.: Am. Heart J. **57**: 552, 1959.
16. Sano, T., Ohshima, H., and Shimamoto, T.: Jap. Circulation J. **21**: 43, 1957; **22**: 153, 1958; Sano, T.: Shindan to Chiryo **43**: 735, 1955; Sano, T.: Saishinigaku **9**: 1344, 1954 (All in Japanese).
17. Young, E., Wolff, L., and Chatfield, J.: Am. Heart J. **51**: 713, 1956.
18. Frank, E.: Circulation **13**: 737, 1956.

Case Reports

A Case of Sinus of Valsalva—Right Ventricular Fistula Successfully Repaired by Surgery

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AMONG the congenital anomalies of the heart, aneurysm of sinus of Valsalva has been considered to be a rather rare disease[1] and only 12 cases were found in 1,000 autopsied cases of congenital heart diseases according to Abbott.[2] About 20 cases have so far been reported in Japan.[3)-10),15)-17)] Since the recent development of the method of temporary cardiopulmonary bypass using pump oxygenator, its surgical treatment has become possible. Although cases of successful operation have been accumulated recently,[12)-14)] such success is still regarded as a rare experience in Japan. We are, therefore, reporting a case of successfully repaired sinus of Valsalva-right ventricular fistula.

Case Report

A 24-year-old male student was admitted to Okinaka Clinic on June 19, 1958 with the chief complaints of exertional palpitation and breathlessness. His birth was not unusual. Development of growth in infancy and childhood was uneventful and there were no subjective difficulties until the age of 14. At 14 years of age, occasional palpitation and shortness of breath appeared during exercise and the symptom gradually became worse. At the age of 17, patient was told that he might have " congenital heart disease " by a local physician. At about the same time, a routine X-ray of the chest revealed pulmonary infiltration in the left. In April 1958, patent ductus arteriosus was suspected on routine physical examination because of the continuous murmur, and hospitalization was recommended for a further study. Palpitation, shortness of breath, and arrhythmia during exercise have gradually become severe in past few years, although the patient remained symptom-free at rest. No episode suggesting the rupture of Valsalva sinus aneurysm has been noticed.

Family history : Father, grandmother and a cousin (female) of father's side had " heart disease ", the details of which were unknown. All three siblings are in good health.

Physical examination at the time of admission revealed a well nourished young male of medium size without cyanosis. Pulse rate was 70–80/min., slightly bounding, with good filling. Quincke's capillary pulsation was positive. No clubbed finger was present. Respiration was normal. Blood pressure was 120/50 mm.Hg

From the Okinaka Clinic, Department of Internal Medicine, University of Tokyo, Tokyo.

in arms and 140 mm.Hg systolic in legs. Cardiac dullness was extended 2 cm. to the right from the right sternal border and 2 cm. to the left from the left nipple line. The upper border was in the 3rd rib. Apical beat and thrill were felt in the fifth intercostal space 2 cm. outside of the left nipple line. Coarse grade IV continuous machinery murmur was best heard at the 3rd interspace on the left near the left sternal border, radiating from the base to the apex. Systolic phase was louder than diastolic. Chest and abdomen revealed no remarkable changes. Neurological examination was negative.

Laboratory findings: Urine and stool were negative. Hemoglobin 108% Sahli, RBC 497×10^4, WBC 6,200 with normal differential count. Serological tests for syphilis were negative. Arm to tongue circulation time was 19 seconds with cholere-tin.

An AP chest X-ray showed a slight cardiac enlargement bilaterally, without protrusion of the main pulmonary artery or increase of lung markings. At LAO, left ventricular enlargement was apparent, without forceful hilar vascular pulsation. ECG revealed deep S in V_1 through V_3, high R in V_4 through V_6, suggesting left ventricular hypertrophy. Phonocardiograph recorded a continuous murmur in the 2nd to 4th interspace along the left sternal border, having the largest amplitude around the 2nd sound, without definite diastolic accentuation. Near the apex, however, the systolic murmur was larger in amplitude than the diastolic. Right heart catheterization revealed no particular elevation of right ventricular or pulmonary arterial pressure. Right ventricular blood contained definitely more oxygen than right atrial blood, indicating a left to right shunt at the right ventricular

Fig. 1 (Left). Chest X ray, anterior position, showing slight bilateral enlargement of heart.

Fig. 2 (Right). LAO position. Hypertrophy of left ventricle is present.

level. Tentative diagnosis of fistualtion to right ventricle of Valsalva sinus aneurysm was made. In order to rule out inter-ventricular septal defect complicated with aortic insufficiency, retrograde aortography was performed. Inserting a catheter from right axillary artery, the catheter was found to enter directly into the right ventricle (pressure 30/0 mm.Hg) from the position immediately above the aortic valve

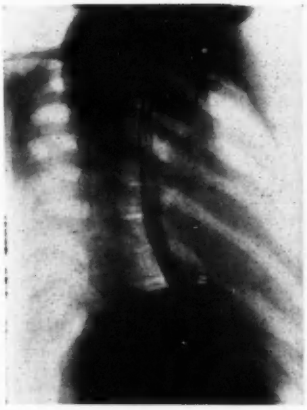


Fig. 3. RAO position.

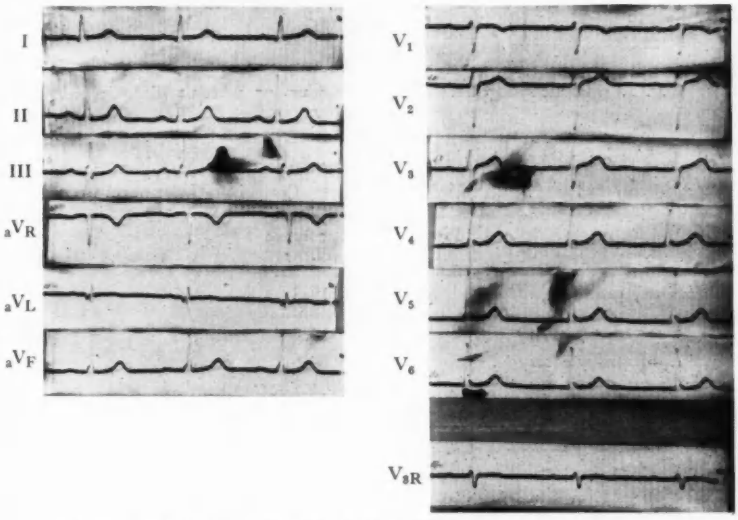


Fig. 4. ECG. Deep S in V_1–V_3, high R in V_4–V_6 suggesting left ventricular hypertrophy.

(125/60 mm.Hg). Fig. 6 represents the pulling out curve from right ventricle to arota, clearly indicating the communication between aorta and right ventricle. This procedure was repeated three times with the same results. Opaque media (Sugiuron) was injected when the tip was immediately above the aortic valve to take serial X-ray pictures, which were interpreted as showing the entry of opaque media to the right ventricle.

Under the final clinical diagnosis of fistula of Valsalva sinus aneurysm to right ventricle, the patient was once discharged on July 20, 1958. In October 1958, the patient suffered from acute hepatitis, and was hospitalized again. The recovery was uneventful and all liver function tests became normal.

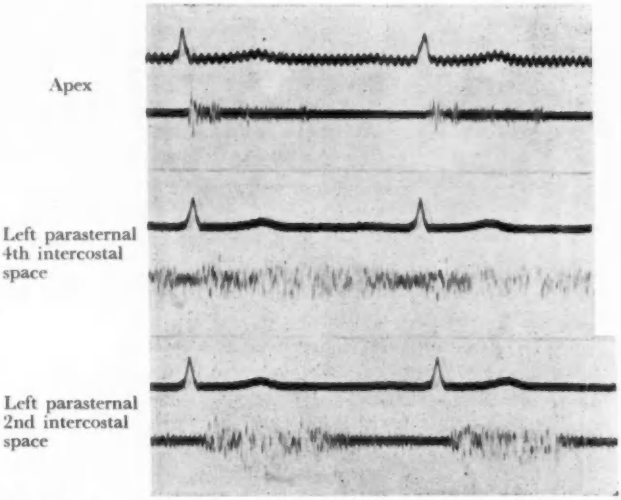
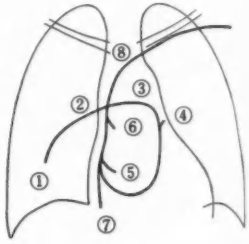


Fig. 5. Phonocardiogram. Continuous murmur without diastolic accentuation.

Table I. Right Heart Catheterization, Indicating Significant Higher O_2 Content in Right Ventricle than in Right Atrium

	Position	Pressure in mm. Hg	O_2 content (vol. %)
1	Pulmonary capillary (wedge)	10/0	19.2
2	Right pulmonary artery		16.3
3	Main pulmonary artery		16.5
4	Right ventricle (outflow)	37/0	17.0
5	Right ventricle (inflow)		16.3
6	Right atrium	6/3	14.2
7	Superior vena cava		14.4
8	Inferior vena cava		14.6
9	Femoral artery		18.3



Pulmonary blood flow 12.9 L./min.
Effective pulmonary blood flow 6.3 L./min.
Left to right shunt 6.6 L./min.

On Jan. 15, 1959, he was admitted to Kimoto Clinic, Department of Surgery, University of Tokyo for the operation. On Feb. 11, under the inhalation anesthesia of N_2O-O_2 with ether, thoracotomy was done at the left 4th interspace, with transection of the sternum. On opening the pericardial cavity, thrill was felt immediately below the pulmonic valve from outside. By the finger inserted into the right ventricle, protrusion of Valsalva sinus aneurysm was palpated.

Following the cannulation of left femoral artery, superior and inferior vena cava were also cannulated through the right atrium. After total cardiopulmonary bypass was completed using bubble-type pump oxygenator of De Wall-Lillehei

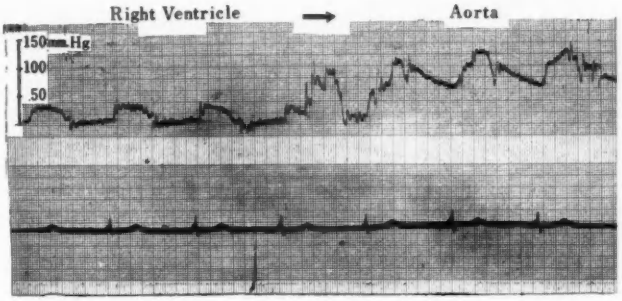


Fig. 6. Pulling out curve of arterial catheter from right ventricle to aorta, demonstrating direct communication between aorta and right ventricle.

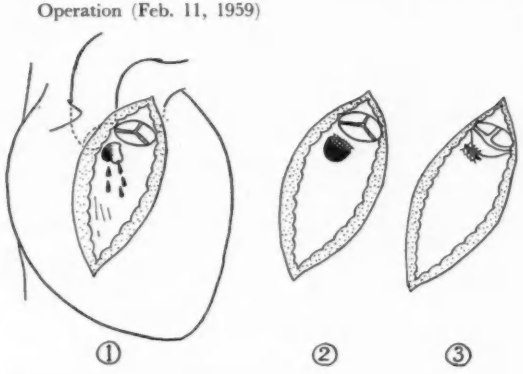


Fig. 7. Operation.

1. Right ventricle opened, aneurysm of Valsalva sinus protruded through IVSD immediately below pulmonic valve. Through the hole at the top of aneurysm, jet of blood streamed.
2. Aneurysm resected and sewn up.
3. IVSD closed.

type, right ventricle was opened. Directly below the pulmonic valve, high interventricular septal defect of 8 mm. in diameter was noted, through which protruded the aneurysm of sinus of Valsalva 15 mm. in length 8 mm. in diameter into the right ventricle. An opening was seen at the top, through which the jet of blood streamed upon loosening the tape on the aorta. First, this aneurysm was resected and closed with 7 stitches, and the IVSD was closed with 4 stitches. Right ventricle was then sewn, cannulae were pulled out from venae cavae and artery, and the chest was closed leaving bilateral drainages. The time of total cardiopulmonary bypass was 18 minutes and 40 seconds.

After 3 weeks, postoperative pleural effusion cleared up and subsequent course was uneventful. Fifty days after the operation, the patient was discharged with the only complaint of slight palpitation after walking. The coarse continuous murmur disappeared postoperatively. A diastolic murmur, however, was heard

Table II. The Cases of Valsalva Sinus Aneurysm in Japan

	Authors	Age Sex	History	Heart sound	Blood pressure	X-ray findings of heart
1.	Kobayashi *et al.* 1944	22 M	" Heart disease " since age 3–4. Exertional dyspnea.	Continuous murmur. DM*>SM* Max. at L. 3–4 ICS.	128/30–0	Enlarged bilaterally. RVH
2.	Sugie 1955	23 M	Congenital heart disease at 4 years. Decompensation since age 15. SBE at age 19.	CM* max. at 4. ICS. L. f.b.* outside of L. sternal border. P_2 accent. DM accentuated.	152/0	Enlarged bilaterally. L. 2nd arc protruded Pulm. congestion. Hilar dance (卅)
3.	Ishihara 1955	39 M	Exertional dyspnea since 3 years. Decompensation since 1 year. Ascites present.	CM max. at 3. ICS 1 f.b. outside of L. sternal border SM>DM. No P_2 accentuation.	156/0	Marked bilateral enlargement. Pulmonary congestion.
4.	Sugiura 1956	28 M	" Valvular disease " during childhood, later congestive failure. SBE since last year.	CM max. at 3. ICS. DM accentuated.	114/40–0	
5.	,,	19 M	At age 17, attack of loss of consciousness with agonizing feeling in the chest. At age 18 similar attack.	SM max at L. 3. ICS. DM slight to the left.		Enlarged bilaterally.
6.	Oguro *et al.* 1957	37 M	" Heart disease " since infancy. Exertional dyspnea.	CM max. at L. 3. ICS. DM>SM.	170/0	Enlarged bilaterally. L. 2nd arc prominent. Pulmonary congestion.
7.	Tasaka *et al.* 1959	52 M	2M ago, acute onset of dyspnea and epigastric pain after running, thereafter exertional dyspnea.	High-pitched DM at the base.	158/0	L. 1st and 4th arc prominent.
8.	Shibuya 1959	33 M	Since boyhood " congenital heart disease ". 1 year ago, precordial pressure feeling, dyspnea.	CM, L. 2–3 ICS. DM>SM.	156/0	Enlarged bilaterally. L. 2nd arc prominent. Pulmonary congestion.
9.	our case	21 M	Since age 14, exertional dyspnea, palpitation. At 17 " heart disease ".	CM max. at L. 3. ICS. SM>DM.	120/50	Bilaterally enlarged.

* DM=diastolic murmur
SM=systolic murmur
CM=continuous murmur
ICS=intercostal space
f.b.=fingerbreadth

(Only those with adequate description are cited)

ECG	Cardiac catheterization	Clinical diagnosis	Course	Final diagnosis
LVH, RVH. incomplete RBBB.	+	Fistula of Valsalva aneurysm (congenital)	unknown	
Left type.	+	Aortic septal defect + PI? or Valsalva sinus fistula?	Died shortly after operation	Rupture of RCS** (3 holes) to RV** + IVSD
Right type. ST depression.	−	?	Died 14 days after admission due to congestive failure.	Rupture of RCS to RV
	−	Rupture of sinus of Valsalva to RV** (congenital)?	Died after 4 months due to decompensation.	Rupture of RCS to RV
	+	high IVSD	Operated.	Aneurysm of sinus of Valsalva+IVSD
	+	Rupture of Valsalva sinus to RV?	Died 1 Y. 8 M. after appearance of symptoms due to congestive failure.	Fistula of right Valsalva sinus +IVSD
LVH. Slight myocardial damage.	−	Aortic insufficiency	Died 9 M. after onset.	RCS and LCS**ruptured into LV**
LVH. RVH.	+	Ruptured aneurysm of sinus of Valsalva to RV?	Died 10 M. after onset.	Rupture of RCS to RV+IVSD +Thickening of R. cusp of aortic valve
Suggestive of LVH.	+	Fistula of Valsalva sinus aneurysm to RV.	Operated and cured.	Fistula of aneurysm of Valsalva sinus to RV+IVSD

** RV=right ventricle
LV=left ventricle
RCS=right coronary sinus
LCS=left coronary Sinus

in the 2nd-3rd interspace along the left parasternal line, which probably represents pulmonary insufficiency resulting from involvement of pulmonic valve during the suture of IVSD.

Discussion

Nearly 20 cases of Valsalva sinus aneurysm have been already reported in Japan, including 12 operated and 7 autopsied cases.[3)-10),15-17)] Table II summarizes those cases provided with adequate description.

Cardiac murmur of this disease resembles that of patent ductus arteriosus, IVSD with aortic insufficiency, aortic septal defect, etc. In the present case, retrograde aortography gave a confirmatory evidence for the diagnosis of Valsalva sinus aneurysm as the tip of the catheter went into the right ventricle. Although Morrow and his associates[33)] reported the passage of catheter through the fistula, the present case was the first case in Japan in which the diagnosis was confirmed by the method mentioned.

Aneurysm of sinus of Valsalva may be congenital or acquired. According to Jones & Langley,[11)] various associated anomalies often accompany the congenital type ; such as anomalies of aortic cusps (15/23), or IVSD (10/23) etc. Negative serological tests for syphilis and the presence of high inter-ventricular septal defect as well as the history seem to make our case most likely that of congenital. Since no episode suggesting the rupture of the aneurysm was known in this case, the fistula might have been present from the birth.

Although successful operations for this defect have been gradually increased in number recently, only 5 cases of survivals[15)-17)] are recorded among 12 operated cases in Japan. Postoperative recurrence of fistula was reported in a case treated only with the suture of IVSD.[16)]

With the recent advances in intra-cardiac surgery under direct vision, a correct diagnosis has become a matter of not only academic interest but practical importance.

Summary

A case of successfully repaired sinus of Valsalva-right ventricular fistula in a young male is presented. Exertional palpitation and dyspnea, slight enlargement of heart, and the continuous machinery murmur maximally heard at the left 3rd intercostal space, were the chief clinical manifestations and signs. Diagnosis was suspected by the right heart catheterization and confirmed with the direct entrance of arterial catheter into the right ventricle from immediately above the aortic valve in retrograde aortography.

Under the total cardiopulmonary bypass, using the pump oxygenator, aneurysm of Valsalva sinus was resected and sutured, and associated high IVSD was also closed. Postoperative course was uneventful.

Brief summary of cases of this disease in Japan is also tabulated.

Acknowledgments

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References

1. Taussig, H. B.: Congenital Malformations of Heart, The Common Wealth Fund, New York, 1958.
2. Sano, T., Hellerstein, H. K., and Keating, D. R.: Clinical Aspects of Congenital Heart Disease, Igaku-Shoin, Tokyo, 1956 (In Japanese).
3. Kobayashi, T. and Shiba, M.: Respiration and Circulation **2**: 298, 1954 (In Japanese).
4. Sugie, S., et al.: Respiration and Circulatio n **3**: 270, 1955 (In Japanese).
5. Ishihara, T.: J. Jap. Soc. Int. Med. **44**: 319, 1955 (In Japanese).
6. Sugiura, M., et al.: J. Jap. Soc. Int. Med. **45**: 653, 1956 (In Japanese).
7. Oguro, C., et al.: Respiration and Circulation **5**: 443, 1957 (In Japanese).
8. Oguro, C.: Jap. Circulation J. **20**: 589, 1957 (In Japanese).
9. Tasaka, S., Koide, K., Ogata, E., and Nakamura, K.: J. Jap. Soc. Int. Med. **48**: 1306, 1959 (In Japanese).
10. Shibuya, M., Ishii, S., Yamaguchi, S., and Kanai, M.: Respiration and Circulation **7**: 509, 1959 (In Japanese).
11. Jones, A. M. and Langley, F. A.: Brit. Heart J. **11**: 325, 1949.
12. Morrow, A. G., Baker, R. R., Hanson, H. E., and Mattingly, T. W.: Circulation **16**: 533–538, 1957.
13. Lillehei, C. W., Stanley, P., and Varco R. L.: Ann. Surg. **146**: 456, 1957.
14. Kay, J. H., Anderson, R. M., Lewis, R. R., and Remberg, M.: Circulation **20**: 427, 1957.
15. Ozawa, Y.: Proc. of the 15th General Assembly of the Japan Medical Congress, April 1959, Tokyo, IV: 495, 1959 (In Japanese).
16. Kimoto, S.: *ibid.* IV: 503, 1959 (In Japanese).
17. Sakakibara, S.: *ibid.* IV: 522, 1959 (In Japanese).

A Case of Idiopathic Cardiomegaly

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SINCE the first description by Josserand and Gallavardin, idiopathic cardiomegaly has been investigated by many workers. Though many etiological factors such as infection, allergy, deficiency of metabolism and intoxication etc. have been discussed, no definite conclusion has been reached to explain its entity. The purposes of this case report are to describe the clinical and pathological findings in a 64-year-old man with cardiac enlargement and a steadily progressive congestive heart failure of three years' duration, and also to discuss the autopsy findings comparing with those of the previous reports.

Case Report

A 64-year-old man was admitted to the Tokyo University Hospital on May 13, 1959 because of exertional dyspnea and chest pain. Prior to this admission, patient was in this hospital in October 1958 for the similar complaints. At that time, patient could not climb more than one flight. A physical examination revealed an enlarged heart and ophthalmoscopic examination showed grade II (Keith-Wagener classification) retinopathy. Series of electrocardiograms in the first hospitalization revealed left ventricular hypertrophy pattern with some ST-depression in left ventricular leads. X-ray and fluoroscopic examinations of the chest (Fig. 1) showed a marked enlargement of the left ventricle with some right ventricular dilatation. No evidence of pericardial effusion was noted. An assumptive diagnosis of arteriosclerotic heart disease was made and patient uneventfully recovered with digitalis and diuretics. He was discharged in January 1959 with maintenance dose of digitalis. The patient was fairy well after the discharge from the hospital and could carry on his daily work. Approximately 5 months before the present admission, patient began to have exertional dyspnea and pressure like sensation under the sternum. There was also occasional paroxysmal tachycardia noted. These symptoms gradually but steadily became severe and at the time of admission on May 13, 1959, he was unable to climb even a few steps of stair. Paroxysmal orthopnea was also present. There had been no continuous chest pain to suggest any myocardial infarction. Physical examination revealed a well developed and nourished man in severe distress. Temperature 98°F, blood pressure 134/98, pulse was slightly irregular with the rate of 106. Respiration was regular but tachypnea of 24. Moderate cyanosis was noted on the face and extremities. Cardiac dullness appeared to be increased more than that in previous examination. At the apex, a gallop was evident. In both bases of lungs, dry rales were heard. The liver edge was palpable 4 fingerbreadth below the right costal margin with moderate tenderness. Laboratory examinations were summarized in Table I. Chest X-ray (Fig. 2) showed

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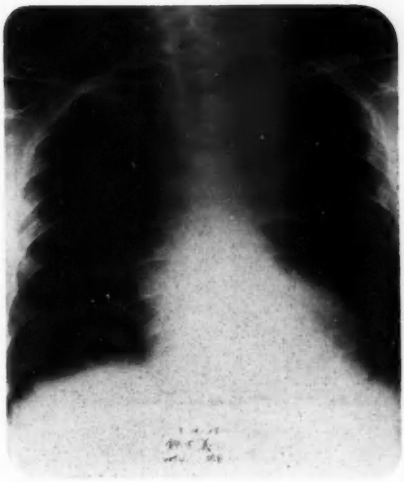

Fig. 1

Table I. Laboratory Data

Serum Wasserman reaction	negative
Blood sedimentation rate	21 mm./I°
Renal clearance test:	
RBF	422 ml./min.
RPF	230 ml./min.
GFR	62.2 ml./min.
FF	0.270
Blood study:	
Hb. (Sahli.)	98%
R.B.C.	498×10^4
W.B.C.	7,800
Hemogramm.	normal no eosinophilia
Urinalysis:	
Albuminuria.	+
Sediments.	red cells 2–3
Venous pressure.	230 mm.H_2O on recumbant position
Circulation time (arm to tongue)	18″–24″
Blood chemistry:	
Total protein.	6.0 Gm./100 ml.
A/G	1.45
NPN	47.6 mg./100 ml.
Urea N	31 mg./100 ml.
Na	136 mEq./L.
K	4.1 mEq./L.
Cl	98 mEq./L.
Total cholesterol	173 mg./100 ml.
Icterus index	4
BSP test (45')	12.5%
Thymol test	7.1
Zn turbidity test	16.0

bilateral cardiac enlargement in greater degree than that of the first. An electrocardiogram revealed an essentially the same finding as before with a transient ventricular extrasystole (Fig. 3). During clinical course, patient was treated with additional digitalis, but no response was obtained. He developed supraventricular paroxysmal tachycardia (Fig.4) and was considered as digitalis intoxication. An intravenous injection of potassium chloride 50 mEq. promptly ceased the tachycardia (Fig.5). The condition of congestive heart failure became progressively worse in spite of intensive treatment with digitalis and diuretic. No steroid therapy was given. Throughout the clinical course, neither temparature nor the sedimentation rate

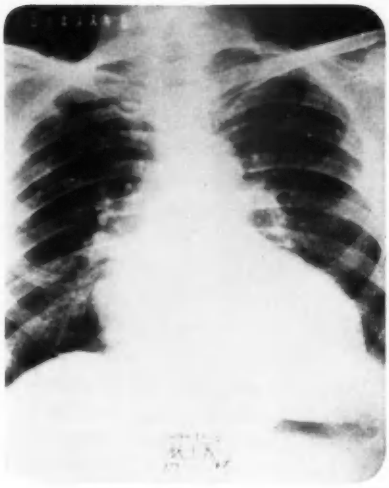

Fig. 2

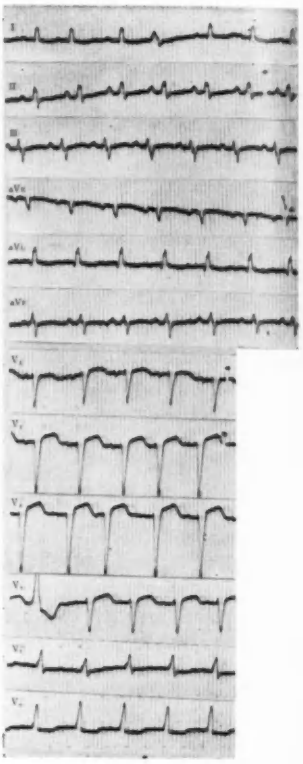

Fig. 3. ECG

showed any abnormality. The patient was found dead in the bed on May 24, 1959.

Autopsy findings: Body weight, 50 Kg. Body height, 143 cm. There was slight edema on the legs. The left pleural cavity contained opalescent, straw-coloured fluid of 200 ml., with a smaller amount of fluid in right without any inflammatory signs. The heart weighed 500 Gm. All chambers of the heart showed slight hypertrophy and marked dilatation. The ventricular muscle measured 1.7 cm. on the left and 0.3 cm. on the right. The left ventricle, as a whole, showed a ball-shape and the trabeculae carnae were flattened. The interventricular septum was buldging into the right ventricular cavity (Fig. 6).

There was irregular, diffuse and greyish-white discoloration of the parietal endocardium of the outflow-tract of the left ventricle. Several scattered, more or less circumscribed, elevations of fibrous plaque were also noted on the mural endocardium of the inflow-tract. A thrombus measured 3×4 mm. was found at apicodorsal portion of the left ventricle. Immediately beneath of this thrombus, an acute necrotic area of approximately the same size was found occupying the inner half of myocardial thickness. In the right ventricle, there was a large confluent plaque on the septum at the orifice of the left pulmonary artery. No abnormal endocardial thickening was noted in the both atria.

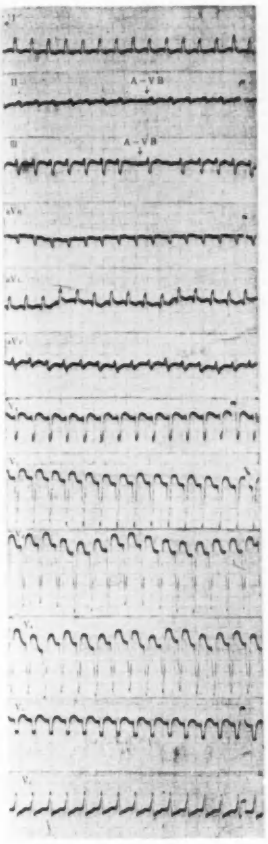

Fig. 4

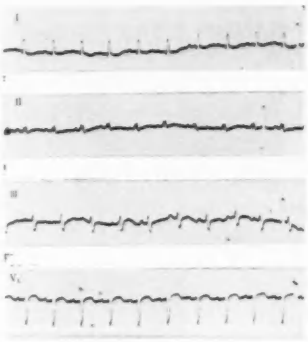

Fig. 5

The valves appeared normal and no congenital malformations were found. The coronary arteries were patent, no visible sclerotic changes were seen. Their distribution was the type of dominant right coronary artery. The aorta showed moderate atherosclerosis.

Pathological changes, other than those in the heart, consisted of congestive changes in the liver, small intestine and kidney, atrophic spleen, and slight congestion in the brain.

Histological examination: In the myocardium of the left ventricle, diffuse, irregular, disseminated and numerous fibrotic foci were found. These changes were especially marked in the inner half layer of the myocardium and there were even acute necrotic or degenerative changes of the muscle fibres with almost the same distribution, (so-called Kämmerchenkettenbildung or myofibrillolysis) but no evidence of cellular infiltration was found (Fig. 7). The nuclei of the muscle fibres were generally greater than usual and markedly pyknotic. The small intramural vessels were markedly dilated and perivascular fibrosis (partially myxomatous) were noted.

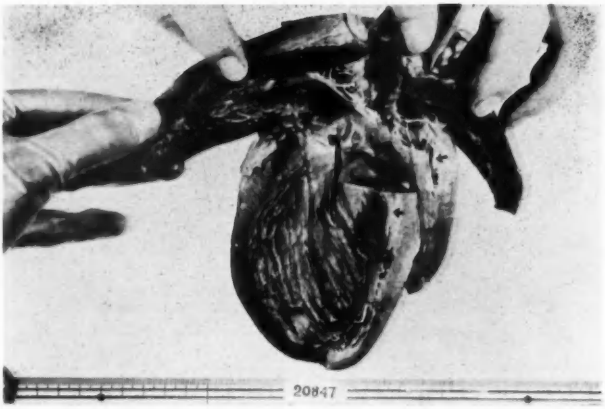

Fig. 6. Marked dilatation of the left ventricle, and irregular diffuse and patchy thickening of the parietal endocardium. (↑).

Apicodorsal subendocardial necrosis and bleeding of the myocardium (⇧) with overlain thrombus.

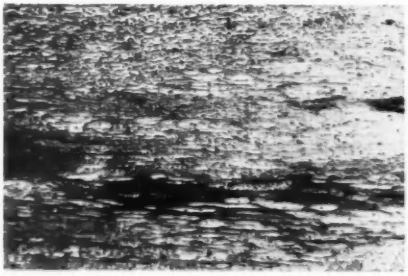

Fig. 7. Irregular focal fibrosis and severe degenerated muscle fibres (myofibrillolysis or Kämmerchenkettenbildung) of the myocardium of the left ventricle. Markedly dilated vessels.

Masson's trichrome stain 50×

There were no sclerotic changes of coronary arteries, anywhere. Beneath the apicodorsal fresh thrombus of the left ventricle, there was a bean sized acute necrosis, which infiltrated into the inner half of the myocardium.

In the macroscopically discolorated portion, particularly in the region of the plaque formation, the parietal endocardium of the left ventricle showed marked fibrous thickening. In this area, increased elastic element played the dominant role in widening the inner connective tissue layer of the endocardium (Fig. 8). In the areas of more or less diffuse endocardial thickening, the elastic fibres were regular and laid themselves parallel to the surface. In the region of the plaque, though meshing with each other to form dense mass, they were shorter and thicker, yet they maintained a general orderly arrangement. The architecture of the outer layers was more or less irregular and was partially lost completely. Beneath the

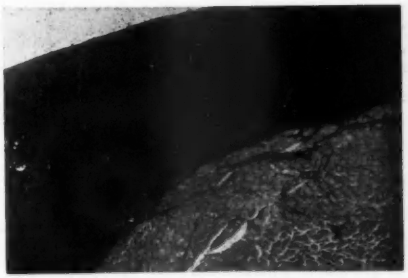

Fig. 8. Marked fibroelastosis of the parietal endocardium of the left ventricle.
Elastica-van Gieson's stain. 100×

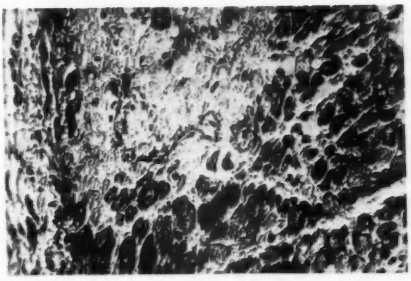

Fig. 9. Focal fall-off of the muscle fibres without cellular infiltration at the interventricular septum.
Mallory-Azan's stain. 200×

elastic lamina, there was an irregular outgrowth of connective tissue which enmeshed with degenerative muscle fibres.

In the interventricular septum, almost the same process and fatty infiltration involved the myocardium including the bundle of Hiss (Fig. 9).

Approximately the same but slightly less changes were found in the right ventricle.

Comments

In recent years, many attentions have been given to a cardiac enlargement with no definite etiology. For the pathogenesis of this kind of myocardial lesion, several theories have been formulated: 1) allergic theory by Löffler, 2) infection theory by Fielder, 3) malnutrition and deficiency theory by Gillanders[16] and Davies,[1] 4) collagen disease theory as described in the reports of periarteritis nodosa,[3,8,17] dermatomyositis,[17] sclerodermia,[8] rheumatoid arthritis, and erythomatodes,[3] 5) intoxication theory by Fossel[18] and Fowler, and 6) a certain anoxic process etc.

In their cases, there presented symptoms and signs of unexplainable heart failure which became resistant to all the treatment as seen in the present case. The present case was clinically diagnosed as an arteriosclerotic heart disease

in view of his age, complaints, blood pressure, electrocardiogram and retinal finding etc.

At autopsy, however, the heart showed marked dilatation and was noticed a diffuse irregular fibrosis of the myocardium with a fibrotic thickening of the endocardium. There was no coronary atherosclerosis found. Concerning the subendocardial necrosis, we are not able to deny the possibility that it might have been due to the ischemia caused by the repeated attacks of tachycardia, namely post-tachycardia syndrome, though we doubt that these attacks would be responsible for the necrosis since the severity of the tachycardia and its duration were not marked in our case.

In previous reports, many different descriptions and terminologies have been given to this disease, but what they all found was some myocardial and/or endocardial fibrosis at autopsy. Most of these previous investigations emphasized certain morphologic characteristics : diffuse endomyocardial fibrosis,[1] diffuse parietal endocardial sclerosis,[2] diffuse endomyocardial sclerosis,[3)-4)] adult form of endocardial fibroelastosis,[5)-7)] endocarditis parietalis fibroplastica,[8] myocarditis with endocardial elastomyofibrosis,[9] obscure or idiopathic nature,[10] myocarditis perniciosa,[11] chronic fibroplastic myocarditis,[12] idiopathic cardiac or myocardial hypertrophy[13] and others.

This case was characterized by diffuse myocardial fibrosis and necrosis, with endocardial fibroelastosis, so its clinical course and anatomic features are closely similar to the case reported by Evans[14] in 1957. From our pathological findings, we made assumption that primary pathological process was the fibrosis of the myocardium and the endocardial alteration was secondary in our case. This has been accordance with those of Flynn,[15] Evans, Lynch, Watt, Comeau and Fisher.

It appears that the myocardial fibrosis is a terminal phase of miscellaneous pathologic process in the myocardium. It is, therefore, very difficult to decide what might be the etiology in this case. In general, the so-called myodegeneratio cordis, as seen in this case, is assumed as a resultant process associated with myocardial failure of miscellaneous origin and it will be almost impossible to determine the etiological factor. But, the patchy myocardial fibrosis in this case, without cellular infiltration or vascular lesion, and acute degenerative change of the muscle fibres, are assumed to be degenerative process occurring in metabolic disorders or in some intoxication, and this degenerative process may be the primary pathogenesis.

Further investigation of this disorder has been on the study.

Summary

A case of 64-year-old male, with recurrent episodes of supraventricular tachycardia and progressive congestive heart failure of unknown origin was presented and discussed.

Markedly dilated heart showed diffuse irregular myocardial degeneration and fibrosis, without arteriosclerosis or valvular lesions, and patchy fibro-

elastosis of the parietal endocardium at autopsy. The pathogenesis has been discussed and it was assumed that it might be a certain degenerative process of muscle fibres themselves.

References

1. Davies, J. N. P. and Ball, J. D.: Brit. Heart J. **17**: 337, 1955.
2. Comeau, W. J.: Am. J. Path. **13**: 277, 1937.
3. Lynch, J. B. and Watt, J.: Brit. Heart J. **19**: 173, 1957.
4. Okada, R., et al.: Respiration and Circulation **6**: 71, 1958 (In Japanese).
5. Auld, W. R. and Watson, H.: Brit. Heart J. **19**: 187, 1957.
6. Dyson, B. C. and Decker, J. P.: Arch. Path. **66**: 190, 1958.
7. Mulcahy, R. and Towers, R. P.: Brit. Heart J. **21**: 567, 1959.
8. Löffler, W.: Schweiz. med. Wchnschr. **66**: 817, 1936.
9. Fisher, E. R. and Davis, R. R.: Am. Heart J. **56**: 537, 1958.
10. Mahon, S. G.: Am. Heart J. **12**: 608, 1936.
11. Boikan W. S.: Virchow' Archiv. **282**: 46, 1931.
12. Chapman, B. M. and Ware, E. R.: Am. Heart J. **33**: 530, 1947.
13. Spodick, D. H. and Littmann, D.: Am. J. Cardiol. **1**: 610, 1958.
14. Evans, B.: Brit. Heart J. **19**: 164, 1957.
15. Flynn, J. E. and Mann, F. D.: Am. Heart J. **31**: 757, 1946.
16. Gillander, A. D.: Brit. Heart J. **13**: 177, 1951.
17. Roulet, F.: Schw. med. Wchnschr. **74**: 427, 1944.
18. Fossel, M.: Beitr. Path. Anat. **107**: 241, 1942.